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XX.—THE APPLICATION OF CUTANEOUS SENSITIZATION TO DISEASES OF THE SKIN *

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Theories of cutaneous sensitization and their application, as advanced by Chandler Walker in the determination of a state of allergy to certain proteins in relation to asthma, have proved of great clinical interest, and when desensitization could be carried out, of inestimable therapeutic value. It is obvious that this method, if applicable to diseases of the skin, would be of assistance in the determination of possible etiologic factors in a large group of them. It is not our object at present to consider at length the various theories of anaphylaxis or sensitization and their application in the cutaneous tests. To enter this maze of literature would, in this instance, occupy unnecessary time and require needless effort. We shall, therefore, limit our remarks to the purely practical aspect of the subject.

To Chandler Walker we are indebted for a method of grouping the various proteins in such a way as to render the determination of sensitization practicable. To determine for ourselves the practical value of this method in the study of various skin diseases, we selected for investigation a large number of diseases, including those that we thought might possibly have some relationship to so-called protein sensitization. The following diseases were studied in this way in an effort to determine their relative cutaneous reaction to various proteins: acne, urticaria, erythema multiforme, lichen urticatus, pompholyx, purpura hemorrhagica, pemphigus, trade dermatitis, dermatitis vegetans and the large eczema group. The method used in carrying out this investigation differed only in minor variations from that employed by others. The protein products were obtained from the Arlington Chemical Company of Yonkers, N. Y., and were made by them under the

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* Studies, observations and reports from the dermatological departments of the Barnard Free Skin and Cancer Hospital and the Washington University School of Medicine, St. Louis, Mo., U. S. A., service of Drs. M. F. Engman and William H. Mook.

directions of Walker. They proved to be reliable products. Lately, we have been using those of Squibb, and of Parke, Davis and Company, with seemingly accurate results.

Patients on whom the tests were made were drawn from the dispensary of Washington University, Barnes Hospital, the Barnard Free Skin and Cancer Hospital and private practice. Confirmatory diagnoses of two or more clinicians were always made before classifying the disease. A detailed history was taken in every case, in an attempt to establish an etiologic clue of a positive sensitization to aid in the first tests. To do this, inquiry was always made as to the duration of the disease and its relation to climatic, occupational, seasonal or other conditions that might possibly have some bearing on the case. If there seemed to be any relation to food, the patient could often assist materially in narrowing the list of proteins in the first test by giving a definite history of exacerbation following the ingestion of a certain food or foods. If there was no seeming associations obtainable in the history, these food proteins were then tested: wheat, milk, egg, beef, pork, and in addition, such others as the case might suggest.

Occupation was always carefully inquired into to determine any possible associations, or to ascertain whether similar conditions were found among fellow employees. Inquiries were also made as to freedom from, or recurrence of, the condition in relation to absence from, or return to, occupation. Climatic influence was always regarded of importance in its relationship to the aggravation or relief of the condition. Attempt was also made to fix a relationship between seasonal foods or pollens. Other associated relationships which it was found necessary to consider constantly were: time (day or night), companionship, focal infections, worry, neurasthenia and unusual traumas. If the patient seemed to obtain relief from any measures employed as suggested by himself, they were often of material assistance in throwing some light on possible etiologic factors, whether due to sensitization, autointoxication or external irritation of some offending substance.

The tests were uniformly made on the inner surface of the forearm. Only exceptionally was it necessary to resort to other parts of the body for this purpose. For each test, a small incision, about 1/8 inch long, was made through the epidermis, with a very sharp von Pirquet scarifier, having a semicircular tipped blade. This form of instrument has no corners but rather a circular cutting edge which, with slight pressure and a rocking motion, produces the least trauma in making the incision. Every precaution should be exerted to avoid trauma in making the incision, as the dermographic or urticarial tendency of some patients is so marked as to interfere with proper development of positive reactions.

These little incisions were placed about 1 inch apart. Each incision was then moistened with a drop of $\frac{1}{10}$ normal sodium hydroxid solution to which there was at once added a minute quantity of the protein preparation to be tested. One-half hour's time was always allowed for the full development of the reaction. Often, however, positive reactions were manifested within a few minutes. Cleaning the surface of the arm in preparing the field for the test was avoided or done an hour or so before the tests were made—a precaution which should be observed, as alcohol or other antiseptic agents influence the reaction. Alcohol particularly tends to reduce the surrounding erythematous areola in positive reactions, in some instances resulting merely in very small wheals or none at all. In very sensitive skins, the friction is sufficient to produce a condition of dermographia, which always interferes with the proper development of the reaction or the interpretation of results. The cleaning of a site was, however, at times necessary, to remove chemical substances that might have come in contact with the skin. This was brought to our attention by observing that, in certain instances in which local therapeutic application had been made to the skin before the tests were made, the proteins failed to go into solution, or were promptly precipitated on coming in contact with the sodium hydroxid solution.

When thirty minutes had elapsed after the incisions were made and the protein applied, the skin over the area was wiped with dry or moistened cotton, and developments were awaited. The results were read according to Walker's method, that is, in comparison with control tests, grading the positive reactions as +, ++, +++ and ++++, and were checked by reaction development measuring $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$ and 1 cm. This graduation, however, will not be used in this report as no constant relationship was found to exist between the intensity of the positive reactions and the clinical manifestations of the disease. Moreover, some very positive reactions consist only of erythematous areolas without the development of wheals.

When this study was first undertaken, it was impossible to secure bacterial protein preparations and only a limited number of pollen solutions were available. The tests herein considered were uniformly made for egg-white, egg-yolk, beef, wheat, potato, milk, bean, horse-dander, with the addition of such proteins as the history of an individual case might suggest, or with less common foodstuffs. Bacterial and pollen tests were not made as a routine, but only in those instances in which the history of the case suggested them. On account of the limited variety of bacterial proteins, tests were made only with those of the *Staphylococcus albus, aureus* and *citreus.* The pollen tests were limited to ragweed, cornflower, goldenrod, timothy and sunflower.

In keeping with the observations of other investigators, subsequent tests frequently yielded positive reactions that had previously been negative.

Tests made at various times differed in the degree of their reaction, which suggests the possibility that the condition of sensitization in individuals may run in the form of cycles in which the line curves in a definite period above or below the normal. This phenomenon is well brought out and discussed by Schloss [1] under the general title of allergy. When a positive reaction occurs with a protein that exists in a number of foodstuffs in a certain group, it will be seen that a person reacting to this protein will probably react in a milder degree to several other proteins of foods belonging to this group; for instance, if sensitization to beef exists, all other meats may also produce a similar but milder reaction. This rule holds good with the proteins of grains, especially wheat, in which there may be a sensitization giving a reaction to the proteins of several other grains.[2] A similar phenomenon occurs with the epidermal protein and the casein group. Confusion frequently arises from this fact and renders the interpretation more difficult, especially in guiding one in the application of diet.

Like all other investigators of this subject, we could not obtain absolute control of our patients and their diet except in a few instances. Unless control is thus obtained, the study is seriously handicapped. It is obvious to every one that it is impossible to control a patient's diet in the large majority of instances, unless he is confined in a hospital provided with a proper diet kitchen, and the directed diet accurately given. Most of our patients were from dispensaries or from private practice, where the absolute control of the ingested foods was impossible. Patients are proverbially thoughtless and sometimes ignorant of the constituents of the foods which they eat. For instance, in a state of wheat sensitization, they would thoughtlessly eat spaghetti or allow flour to be added to gravies or soups, thus invalidating the wheat-free diet. Unless proper inquiry into every article of the diet list was made by the physician in attendance, well controlled results could not be obtained. In the case of infants, the elimination of one or more proteins from the diet was easier, since the patient's own choice of food was not a factor, and with the cooperation of an intelligent mother in the matter of such simple diet, absolute control could in most instances be obtained.

Improvement under dietetic control, followed by exacerbation on return to the diet containing the suspected proteins, will always indicate,

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1. Schloss, O. M.: Allergy in Infants and Children, Am. J. Dis. Child. **19**: 433 (June) 1920.

2. The work of Osborne and Wells might be commented on at this point. Theirs were the first studies on protein relationships.

with a fair degree of certainty, the tolerance of the patient, which may vary from absolute intolerance to the allowance of a considerable quantity of the offending food.

TESTS AND RESULTS

1. *Acne.*—Eighteen cases of acne vulgaris were used for this test without any specific result. Sixteen of them were negative; two suggested slight positive reactions to wheat and fish, which shows a negation in summing up the results obtained in this disease.

2. *Dermatitis Herpetiformis.*—This disease is undoubtedly due to some form of toxemia. One of us (Engman) has demonstrated several times the close relationship that seems to exist between this affection and intestinal putrefaction. Focal infections in the teeth or at other sites may be etiologic factors. Drugs have been known to precipitate dermatitis herpetiformis, as pointed out by Hartzell and Engman. For instance, in the administration, under special conditions, of potassium iodid to susceptible persons, a definite eruption of dermatitis herpetiformis characteristic in its clinical and histologic phases may result. If dermatitis herpetiformis is caused in certain susceptible persons by the administration of drugs, it shows definitely a drug genesis, using the word in the broadest sense. Therefore, other toxemias or toxic bodies circulating in the blood stream may precipitate an attack. In this study, eleven cases typical of the disease were investigated, in which only one gave slight reaction to horse dander, a protein which obviously produces its greatest damage through external or local influence, causing dermatitis.

3. *Urticaria.*—The etiologic factors in producing this large group of diseases may be divided into two classes, both of which are blood-borne: (1) by the distribution of emboli or micro-organisms; (2) by the contamination of the blood stream by some chemical body admitted into the body through foodstuffs, the action of micro-organisms, intermediary metabolism, or other sources or foci from which toxic bodies may emanate. In the latter subdivisions, we must include parenteral introduction of protein, as in serum disease.

It is in this large group of diseases, obviously of toxic origin, that we should obtain very interesting and instructive results from cutaneous sensitization. We must admit that the offending toxin, whatever it may be, produces the eruption by a specific action on the cutaneous capillaries, and not on the vasomotor centers or indirectly through the vasomotor nerves. All histologic pictures of this group show definite symptoms of inflammation, as pointed out by von Duhring, Philipson and Gilchrist.

Nineteen patients were investigated, fifteen of whom reacted in some manner to this test: five to egg-white, one to salmon, six to wheat, two to cheese and one to beans. All of these were cases of urticaria of the usual type, and very satisfactory therapeutic results were obtained whenever the diet could be controlled absolutely. Two cases were particularly interesting. One was an iron-worker who had had chronic urticaria for many years. The least trauma would cause enormous wheals to appear, and the resulting factitious urticaria would so handicap the patient that he had to discontinue his work. He showed a marked cutaneous sensitization to wheat, and as we were able to control his diet, wonderfully satisfactory results were obtained. At various times he tested his own susceptibility by eating wheat, with the inevitable recurrence of the traumatic urticaria. Gradual return permitted the inclusion of whole slices of wheat bread. He could also eat toast and cereals, when they were thoroughly toasted.

Another patient, a woman, aged 45, in whom chronic urticaria had existed for many years in the ordinary traumatic variety, was found to be very sensitive to casein. She had been put on various diets and had been treated by some of our leading gastro-enterologists, with no relief from the chronic urticaria. As it happened, a cutaneous test had not been made before. Through this test, it was demonstrated that the patient was sensitive to casein, cheese and milk, and when these articles were eliminated from the diet, excellent results followed. Boiling the milk and skimming off the coagulated casein did not seem to act favorably in her case.

In this urticarial group were several patients with the ordinary type of sensitization to egg-white. Of all varieties of proteins, egg-white and wheat seem to be the ones to which the largest number of these patients react. All of these improved under proper restriction of diet. In some, a return to the offending food produced exacerbation.

4. *Erythema Multiforme.*—Of the pure Hebra type of erythema multiforme, six patients were tested, all with negative results. Several of these were tested many times.

5. *Lichen Urticatus.*—Four patients were tested, two of them several times, with negative results.

6. *Pompholyx.*—Four patients were tested, with one positive result. This patient shows pork sensitization up to the present time, and obtains prompt relief by elimination of pork from the diet.

7. *Pemphigus.*—Two patients were tested, with negative results.

8. *Purpura Hemorrhagica.*—Three patients were tested, with negative results.

9. *Trade Dermatitis.*—We have herein included those cases of dermatitis due to occupation, such as that found in cement workers, chem-

ical workers, dentists, etc. There were nine patients tested, all of whom were negative to protein sensitization.

10. *Dermatitis Vegetans.*—One patient was tested, with negative results.

11. *Eczema.*—We have now come to the group of diseases that are supremely interesting from the standpoint of cutaneous sensitization, namely, that large group of diseases known by the generic term eczema. It is not necessary here to enter into a discussion of the nomenclature or the pathology of the members of this group. First, for the sake of convenience, and to avoid confusion, we will convey the clinical picture according to the present nomenclature, using terms familiar to all in the designation of types.

(a) Erythematous Eczema: Seven patients were observed who were of extreme interest in relation to cutaneous sensitization in its broadest aspect. Six of them were free from any detectable protein sensitization, yet their skins were peculiarly irritable and reacted to the slightest traumas, such as wind, dust, sunlight or any other slight influence.[3]

One was sensitive to oak pollen and had suffered from erythematous eczema from this source for nine years. It began in April, lasted through the spring, and was accompanied by typical attacks of hay-fever. Later, under the care of Chandler Walker, the patient obtained relief through desensitization.

(b) Chronic Eczema of the Generalized Type: There were twenty-one patients, eight of whom showed cutaneous sensitization: one to *Staphylococcus aureus,* four to wheat, one to egg, one to wool and two to horse dander.

(c) Localized Eczema: These eczemas were localized on the flexor sides of the elbows or knees, etc. Two patients were negative, and one was positive to wheat.

(d) Acute Eczema: It was found on examintation of the patients with acute eczema that none was sensitive to any of the proteins that we had on hand, which proved that most of the very acute forms of eczema were due to purely external chemical causes, such as hair dyes, fur dyes, cleaning fluids, cosmetic, medicines, linaments, or other sources of acute dermatitis, including various poisonous plants. One peculiar case of erythematous dermatitis was that of a man who suffered strange attacks of a recurrent dermatitis of the face On investigation, his condition proved the result of a bleach that his wife used for her hair, which affected his skin as he rested his cheek against her hair or against the pillow that she had used.

3. Two of these patients were probably photosensitive, or were the hematoporphyrin types of Hausman.

REPORT OF CASES

CASE 1.—M. S., a girl, aged 16, had had relapsing attacks of eczema for some years due to *Staphylococcus aureus*. She was easily desensitized with great success by *Staphylococcus aureus* vaccine in increasing doses.

CASE 2.—A girl, aged 15, had had eczema since babyhood. Her case belonged, no doubt, to that class which Czerny has called exudative diathesis, eczematous attacks recurring frequently throughout life. She was only partially benefited and then when in the confines of the hospital. Had it been possible to obtain the full cooperation and confidence of the patient, we are certain, judging from our short experience with the case, that the results would have been brilliant.

CASE 3 (common).—A man, aged 54, had had a chronic dermatitis or eczema on the face, hands, neck and ears, almost continuously for four or five years. The eruption at times disappeared, and then returned within a few hours, characterized by a tingling sensation, accompanied by erythema and edema of the area affected, always followed by itching, exudation and dermatitis. He had no knowledge whatever of food sensitization, and his reaction to wheat, at the time of observation, was weak. As he was an intelligent man, he cooperated and excluded wheat from his diet, which was practicable only when he was not away from home on his customary trips. Under these conditions, he was completely relieved of all symptoms.

CASE 4.—J. H. D., a woman, aged 56 years, had a dermatitis of the face and forearms, almost of the vesicular type, which had troubled her for years, disappearing and reappearing at times. She had strong sensitization to wheat, but under proper diet, she rapidly improved.

CASE 5.—C. D. D., a woman, aged 30 years, had a very severe erythematous eczema of the face, forearms, neck and scalp. The attacks came before we began this investigation. The patient lost all the hair of the scalp, and recovered very slowly. She did not, however, remain perfectly well, until we discovered her sensitization and then placed her on a diet. She stated on April 12 of this year that when she ate bread or wheat in any form, the skin of her face became erythematous and swollen, accompanied by intolerable itching. Rye bread then replaced wheat bread in her diet, and her physician ordered a new cereal, in which, however, wheat was detected by the violent cutaneous reaction within two hours after eating.

CASE 6.—All the symptoms of an eczema in a physician, who had a sensitization to wool protein, were alleviated when he discarded woolen underwear.

CASE 7.—A huckster, aged 35 years, was sensitive to horse dander, and because of his constant exposure to his horses, he suffered with continuous dermatitis. Owing to his occupation, we were unable to obtain satisfactory results, but we are now attempting desensitization.

CASE 8.—W. L., an oil speculator, aged 33 years, who had had erythematous eczema for fifteen years, was very sensitive to horse dander. His condition had the same history as all the other cases of this type, becoming better at times and remaining so for some months, then reappearing suddenly over night. When his attention was called to horse dander, the reason for his attacks became clear to him, and he remembered that his first attack occurred at the time he had a pet dog of which he was fond and accustomed to handle a great deal. He also recalled subsequent attacks on visits to horse sales or stockyards. He is now being desensitized. (It is curious to note how animal dander

from almost any animal may cause an outbreak of symptoms in those sensitized to any of them.) Through the patient's own observation, he relieved his itching at night by removing feather pillows and woolen blankets.

CASE 9.—G. R., a man, aged 50, had complained of eczema every summer for the last five years. In winter, his skin was clear, and the patient thought it was entirely normal. At the time of the first visit, his entire face, neck, ears, arms and hands were covered with an exudative crusted eczema. His lip was drawn and covered with crusts. At first, he gave a very doubtful reaction to tomato pollen. Further inquiry elicited the fact that the present skin condition superseded the setting out of young tomato plants. Tests were repeated in about six days, using juice from tomato vines. These resulted in a very positive erythematous reaction that developed slowly, however, and was developed only after twenty-four hours. This reaction was not an urticarial lesion but a distinct red pin-point vesicular eruption about 1 cm. in diameter.

(e) Infantile Eczema: This is the bête noire of all dermatologists. It was with great interest that we approached this part of our study and the results have been both satisfactory and unsatisfactory: satisfactory as far as the tests gave a clue to the etiology of the condition, but most unsatisfactory as far as control and outcome of treatment were concerned. The type of disease, so well described by Czerny as exudative diathesis, stands out as typical for most of those infants who have eczema. The disease usually begins on the face as an erythematous blush and extends to the extensor surfaces of the extremities. If the baby be not carefully watched and be allowed to scratch or rub the parts, the entire body not infrequently becomes involved. Four cases of infantile eczema which localized persistently in portions of the body other than the face or extremities, were excluded from this study because irritation of various kinds in these areas obscured the picture.

Of the exudative type (thirty-six in number), 78 per cent. responded positively to some protein sensitization: nine to egg-white (only), two to egg-white and milk (cows), six to milk (mother's only) five to milk (cow's only) and six to wheat (only).

Unfortunately, the majority occurred in dispensary practice, and therefore were uncontrollable as to diet. But in those cases in which we were able to encourage or receive cooperation on the part of the mother, brilliant results were obtained.

REPORT OF CASES OF INFANTILE ECZEMA

CASE 1.—S. B., aged 4 months, had the usual dermatitis. The cutaneous test showed a reaction to mother's milk. When put on proper feeding, the patient immediately responded, the itching subsided, and the eruption disappeared. After a period of some weeks, there was a relapse, and after another test, the baby was found very sensitive to beef protein. The diagnostic accuracy of this test was substantiated when the mother confessed to having fed the child beef tea. The baby at this time showed sensitization to both milk and beef. On discontinuing the beef tea, the skin condition immediately cleared.

CASE 2.—M. B., aged 5½ months, reacted positively to cow's milk. It was suggested that goat's milk be tried, and the eruption disappeared coincidently. Because of the previous condition of the child, which had caused the mother considerable worry, she was advised to place it in a hospital for a while. While in the hospital, the child was again fed cow's milk, and a severe relapse of the cutaneous condition followed, and when it was once more put on goat's milk, this condition subsided. It is interesting to note that when the mother was in the hospital, an eminent pediatrician attempted to feed the child on a proper modification of cow's milk, but without success, the intense pruritus and eczema relapsing.

CASE 3.—F. J. B., a boy, aged 2½ years, had a typical case of exudative diathesis. The cutaneous test showed a doubtful egg-white reaction. As the child had been eating eggs freely, it was put on an egg-free diet with rapid and brilliant results. Within a few days the face was almost free from the eruption.

CASE 4.—J. K., a girl, 3 years old, presented a severe case, which had begun shortly after birth. The skin of the face and extremities was thickened, yellow, pasty and showed patches of eczema. The glands at the angle of the jaw and in the neck were enlarged. The child was a mouth breather, a condition which would probably continue for years unless the cause was discovered and eliminated. The child proved distinctly reactive to wheat. Fortunately, in this instance, we had the cooperation of a very intelligent mother. The baby appeared for treatment on April 2, 1919, and was completely well on May 23, 1919. She was presented at the joint meeting of the Chicago and St. Louis Dermatological Societies in October, 1919, and not the slightest symptoms of her former disease were to be found. The enlarged glands had disappeared, her skin was soft, pink, smooth, healthy and beautiful. Strange to say, even the mouth breathing had disappeared. The mother stated that if the child was given a cracker, for instance, for breakfast, in the afternoon she would begin to scratch and rub her skin because of erythematous welts that appeared on the cheeks and extremities.

We might say in passing, that pruritus of the face and extremities seems to be the first symptom produced by the disturbing protein. Thus, traumatism is induced at the sites of the itching by rubbing and scratching, which establishes a dermatitis that is usually increased by local agents, such as staphylococcic infections, lotions and salve. In some instances, distinct erythematous blotches, or wheallike lesions, seem to precede or cause the intense itching. Some of these children madly toss themselves from side to side in paroxysms of itching. When the itching is produced by some sensitizing protein, the pruritus is in many instances wonderfully and quickly relieved by the removal of that protein from the diet.

The four cases just described have been quoted for illustration. It is needless to continue with other such cases, as the literature now presents many of them. Our studies lead us to believe that of the 78 per cent. in this group, showing protein sensitization, all could have been brought to a satisfactory therapeutic conclusion, had we had absolute control of the diets. This being the fact, the future treatment

of infantile eczema depends: first, on the accuracy with which the cutaneous sensitization test is performed and interpreted; second, on the accuracy in following the therapeutic path which that interpretation directs; third, on repeating tests at intervals to determine the exact status of the case in relation to protein sensitization.

SUMMARY AND CONCLUSIONS

1. In urticaria, 79 per cent. showed a positive sensitization; in infantile eczema, 78 per cent. and in chronic generalized eczema, 38 per cent.

The percentage is almost negligible in such diseases as dermatitis herpetiformis, erythema multiforme, lichen urticatus, pemphigus and purpura hemorrhagica, although one might say that a sufficient number of cases of the latter diseases had not been investigated.

2. The necessity of a thorough investigation of cutaneous sensitization is shown in the first four conditions.[4]

3. This study presents an interesting comparison with that of Baker,[5] who, under the title of "Incidence of Protein Sensitization in Normal Children," showed "that the incidence of positive protein sensitization in normal children is negligible." This emphasizes the significance of the high percentage we have obtained in eczematous children, and corresponds with the statistics of Blackfan, who showed a protein sensitization as high as ours in infantile eczema. Blackfan goes further and states that children without eczema rarely give a positive test.

4. From the excellent results obtained in so many cases in this study, we are forced to the conclusion that the cutaneous sensitization tests by the dermal method is of inestimable value as a diagnostic and therapeutic measure in the study and care of urticaria, eczema and several other diseases of the skin.

5. It is obviously necessary that a study of a case, from the standpoint of protein sensitization, must include those proteins with which the patient may come in contact in his daily life, an extremely laborious study and one that requires time and patience.

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4. We should like to call attention to the fact that we were not able to carry out extensive studies with bacterial and pollen proteins in our early cases, though now complete lists of products are available. Also, that no special proteins were prepared for study of special cases, which (obviously) should be done, if full value is to be derived from this diagnostic method.

5. Baker, H. M.: Incidence of Protein Sensitization in Normal Child, Am. J. Dis. Child. **19**:114 (Feb.) 1920.

6. From the therapeutic standpoint, the physician is greatly handicapped by not having complete control of the patient's diet, which, however, has nothing to do with the method from its purely diagnostic application. Our efforts have given us, we might say, in every instance in which we could exercise control, the most excellent results, and, when desensitization was possible, the diet in many instances could be resumed.

7. We have not at present sufficient experience with desensitization to speak dogmatically of its merits, yet we believe from this experience that it has as great a future in the cutaneous field as in that of asthma and other affections of the air passages.

OCCUPATIONAL DERMATITIS IN DENTISTS: SUSCEPTIBILITY TO PROCAIN

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Occupational dermatitis in dentists has usually been laid at the door of some one of their antiseptics, or soaps, or in an indefinite way referred to some one of the many substances which they handle. Frequently the patient, a dentist, is informed that sooner or later experience will show the particular agent which is causing his condition. An examination of the textbooks and literature does not reveal, except in one instance, any evidence of a dermatitis associated with local anesthetics. Mook,[1] in a recent paper, has reported the case of a dentist with susceptibility to apothesin, and in reporting this case states that procain gave much the same reaction as apothesin when skin tests were applied. The dermatitis in this case, however, cleared up when the use of apothesin was stopped. The attention of the profession has apparently not been called to the fact that procain may be an etiologic factor in some of these cases. It is the factor, without doubt, in the three cases which I have to report. These dentists, who have practiced for a number of years, who have used procain over a period of months, have had an irritated condition of the hands, which appears to be due to their individual susceptibility to procain. This dermatitis did not develop immediately when they began to use the drug, but appeared after it had been employed by them as a local anesthetic over a period of months.. This fact may be interpreted as an indication that the condition was fundamentally an acquired susceptibility rather than a real idiosyncrasy—a susceptibility of unexplained or idiopathic origin.

The fact that procain can be added to the list of substances which are the cause of cutaneous manifestations in susceptible persons warrants a few statements about the drug. Procain was introduced by Einhorn, and was clinically tested and exhaustively written about by Braun in 1905. It was most widely used among dentists, and also for local anesthesia in surgery. It was introduced into this country about 1912, and is apparently the local anesthetic most widely used among

1. Mook, W. H.: Skin Reactions to Apothesin and Quinin in Susceptible Persons, Arch. Dermat. & Syph. **1**:651 (June) 1920.

dentists, and also for local anesthesia in surgery. It has numerous advantages over cocain. It is six or seven times less toxic; it will keep for a long time without deterioration; its action is increased and prolonged by combining it with epinephrin; it does not cause the least irritation on injection; it is soluble in its own weight of water. Le Brocq makes the statement that it is equal to cocain in its anesthetic properties. Gwathmey is responsible for the statement that after absorption the general effect on the system is scarcely perceptible, neither the circulation nor the respiratory system being affected. There is no mydriasis, no disturbance of accommodation, and no increase of intra-ocular pressure. It is neutral in reaction, and its solutions are precipitated by alkaloids and alkaline carbonates, although it is not affected by sodium bicarbonate. It is apparently a much more satisfactory drug to use than cocain.

The three dentists whom I have seen recently because of a dermatitis of the hands have been in practice for many years, and have been using procain for some months. The eruption on their hands has appeared since they began to use this drug. Since discontinuing its use, or wearing gloves, the irritation has disappeared and their hands have become normal. Furthermore, the evidence of skin tests has been in agreement with the clinical evidence.

REPORT OF CASES

CASE 1.—Dr. A. has practiced dentistry for twenty-three years. He has used procain occasionally for one year, and exclusively for two years.

History.—In May, 1920, itching began between the fourth and fifth fingers on the right hand, which gradually extended to other fingers; the fingers became red and fissured, and there was some oozing. Itching had been most intense at times.

Examination.—Examination in July showed considerable scaling, with fissuring of both palms and about the fingers. There were circinate, almost serpiginous areas with numerous scales, considerable redness, and a suggestion of vesiculation. There was much redness between several of the fingers, and there was a deep fissure between the fourth and fifth fingers on the right hand, and a fairly deep fissure at the base of the fourth finger on the palmar surface, in addition to other less active fissures. The condition of the right hand was much worse than that of the left hand, especially on the ulnar side. The palms, at this visit, gave the impression of an epidermophyton infection. Examination of the scales was negative, but the clinical appearance warranted the use of half-strength Whitfield's ointment. Examination of the scales at the end of twenty-four hours in potassium hydrate solution revealed no mycelia, but there were numerous highly refractile bodies suggesting spores.

Course and Treatment.—In two weeks there was distinct improvement, both objectively and subjectively. The itching became less, and the fissures healed, leaving only slightly scaly and red areas between the fingers and the sites of former open fissures. The skin became more normal. An area of vesiculation and redness appeared about the nose, right cheek and lip, which at this time

was thought to be caused by the irritation which resulted from the transference of some of Whitfield's ointment to the face.

At the end of two weeks more, new areas had appeared on the hands, areas which were more vesicular and grouped, with recurrence of fissures and burning and itching, especially on the middle and forefingers of the left hand. At this time inquiry was made into the chemicals which the patient was using, particularly the ones which he had begun to use most recently. At this time procain was suggested as a possible cause, and he was advised to use rubber gloves during his work, and to alternate between a weak Whitfield's and Lassar's paste. His hands became better, the fissures closed, and there remained numerous areas of dry, scaly skin, with few fissures which were dry. There was no redness and no vesicles, and the itching had gradually disappeared.

Skin Tests.—Six weeks after his first visit skin tests were made on his forearm with the solution of procain which he customarily used. It contained procain, 2 per cent., in Ringer's solution, with a slight amount of chloretone as preservative. The tests were performed, using this solution, with and without suprarenal extract, and using an old solution made up ten days or two weeks previously. In twenty-four hours there was intense redness and itching at the points of inoculation with all procain solutions. The old solution gave the greatest reaction, showing a rather intense red area, 1 cm. in diameter, elevated, with severe itching. Controls were negative.

At this time he went on his vacation and on his return in three weeks reported that his hands were normal while away, even though subjected to fairly hard usage. They were just as well as ever on his return to work. He has continued using procain solution, but has worn gloves when using the solution. In spite of this fact, he has one or two small fissures on his hands, and there is occasionally more or less itching. He has had slight irritation and redness about the right corner of his mouth, and recalls squirting some of the procain solution on his face several days before. The previous irritation on his face probably resulted from a similar accident. On his forearm there are still redness and slight thickening of the skin at the site of previous inoculations the point of application of the old procain solution showing as a distinctly purplish area about 1 cm. in diameter. Itching and redness persisted, the patient states, for two weeks after inoculation.

Another series of tests was made in confirmation of the first series, using the same solution as previously, using suprarenal tablets alone, and using cocain solution. At the same time a similar series was performed on my own forearm, the results of which were all negative. The results were absolutely confirmatory, similar reactions being produced as at the previous tests. An additional fact of interest at this time was that after the solutions had been applied about fifteen minutes a sudden motion of the patient's forearm spilled the solutions to the inner side of the forearm. Evident traces of the solution were found for many days over the areas which had been covered in the spilling. Severe itching and redness and distinct streaks were produced where the procain solution had traveled. The use of procain had been given up and the hands were practically clear save for slight scaliness in patches, and one or two dry fissures. No new lesions and no new vesicles had appeared.

A third series of tests was made on the forearm, using six solutions: (1) Ringer's solution; (2) procain E (Metz), 2 per cent., with epinephrin; (3) procain F (Metz), 2 per cent., with epinephrin; (4) procain T (Hoechst), with epinephrin (different make); (5) cocain, 1 per cent., with epinephrin, and (6) sterile water. Within twenty-four hours there were redness and eleva-

tion about 2, 3 and 4, greatest about 3. There was the same intense itching, with redness extending for 5 mm. about the region of inoculation, with slight elevation, the whole process, and the redness, lasting for nearly two weeks.

CASE 2.—Dr. B. has practiced dentistry for thirteen years and had used procain two years before symptoms appeared.

History.—In November, 1919, he began to have redness of the skin about the nails, with fissuring of the nails and adjacent skin and itching, especially of the left hand. Later a similar condition appeared between the fingers and on the palms. The left hand had always been most severely affected. The process had always been more localized about the fingers and nails than elsewhere. There had been itching and oozing, with much serum exuding at times. The nails had been rough, cracked, corrugated, with some suppuration, both at the base of the nails and below the nails at the finger tips. He had been using Whitfield's ointment part of the time, and had been careful in regard to the use of soap. For one period of three or four weeks, and for several shorter periods, he had been unable to work because of his hands.

Six days before his visit to my office in October, 1920, he was told by Dr. A. (referred to in the preceding case report), of the possibility that procain might be the causal agent. At that time he had fissures beneath the nails at the tips of the first and third fingers on the left hand, and about these two nails especially, together with severe general itching and burning of the hands. At that time the right hand had much the same feeling with areas of redness and oozing on the approximating surfaces of the third and fourth fingers. He gave up the use of procain on this date, and he stated that the itching and burning had become gradually less and that the hands had become drier and less red.

Examination.—On the day of the examination, six days after stopping the use of procain, the left hand showed considerable fissuring about the nails, with redness and exfoliation below the tips. The skin at the bases was thickened and rough as in a chronic paronychia. The first three fingers were dry, rough and scaly. The last two fingers were nearly normal. On the right hand the nails were much better than on the left, but were rough and more or less corrugated and dark colored. Between the third and fourth fingers there was an area of redness on the fourth finger, with slight vesiculation on the side toward the third finger. There was also a small, red, crusted area on the dorsum of the fourth finger just behind the nail where the ball of the third finger rested while working. His position at work, holding an instrument, showed closer approximation and pressure on the spots mentioned. On the right forearm, near the wrist, on the palmar side, was a small papule where procain had been dropped about five days previously. The patient also gave a story of accidentally squirting some of the solution from the needle on his face, near the nose, some time ago, followed in from twenty-four to forty-eight hours by intense itching and redness.

Course of Disease.—Five days after his first visit, his hands showed much improvement. The left hand showed practically all normal skin. There were no signs of the previous condition about the middle finger nail. The right hand was all clear except on the thumb side of the fourth finger where there were a few small papules, dull red in color, which were not itching. The area on the dorsum of the fourth finger had disappeared entirely. The patient stated that he must have washed his hands forty times the day before as a matter of experiment, but his hands seemed no worse. He was still continuing to use cocain for extraction.

Skin Tests.—At this time skin tests were performed with (1) sterile water; (2) procain, 2 per cent.; (3) apothesin, 2 per cent.; (4) cocain, 2 per cent.; (5) a solution containing procain and epinephrin in Ringer's solution (solution four or five months old); (6) procain, 0.5 per cent. These solutions were applied and allowed to remain for thirty minutes. In twenty minutes a definite wheal, irregularly 5 mm. in diameter, appeared about number 2. About number 6 was a similar blanched area, but only 2 mm. in diameter. About number 4 was a slightly red area with slight elevation. The other areas simply showed a redness at the point of rotation of the dental burr. In twenty-four hours there was a distinct red papule about number 2 and number 6, with considerable itching. In forty-eight hours there was at number 2 a red papule, 5 or 6 mm. in diameter. The redness was rather intense, and there had been much itching about this particular inoculation. There was a slight redness and elevation for an area 3 mm. in diameter about number 5. About number 6 there was a slightly larger area of redness with a little more elevation. All of these had itched to some extent but not as much as number 2. The patient discontinued the use of procain and his hands have remained normal.

CASE 3.—Dr. C. has practiced dentistry for seventeen years and had used procain from two to three months before symptoms appeared.

History.—In August, 1919, Dr. C. began to have itching and burning of the hands, with considerable redness and the formation of blisters on the backs of the hands and between the fingers. At this time he had to give up work for three weeks on account of his hands. He had had urticaria occasionally but that is the only previous skin trouble which he had had. He began the use of "Novol," a procain preparation in Ringer's solution, about two months previously, in May or June, 1919. He dated the disturbance approximately to the time when he began to boil frequently this anesthetic solution for use. He believed that his hands became affected from the steam.

When he returned to work his hands were scaly, without any itching or redness. Within five days recurrence occurred, and he was away from his office for another period of three weeks. This time when he returned to his office his hands were in much better condition and practically normal. Three days after his return to work his hands became affected again, and at this time his face was much swollen and red, with considerable crusting. It was necessary for him to give up work for a period of three or four weeks. During the period when the disease was at its height the nails were discolored, brownish, cracked, and became separated from the bed, and later came out altogether. His hands were very greatly swollen, so that it was impossible to approximate the tips of the fingers. The area of involvement never extended above the edge of the coat sleeves and was only slight on the palms. The condition of both hands was about the same.

In the latter part of October he started to use rubber gloves all the time in his work and remained practically free from any skin disturbance of his hands. Since March, 1920, he has been wearing gloves in his practice only while using procain, and his hands have remained clear.

About three weeks before coming to my office he had not used his gloves for one day because his hands had been well so long. On this day he used procain on five or six patients, and two days later the second and third fingers of his left hand were much fissured, red, and oozing. He has returned to the use of gloves during the actual injection of procain, but he removes the gloves after injecting the anesthetic and putting away his instruments.

At the present time the first two fingers of the left hand are the only ones which show any variation from normal. Near the tips are red, slightly fissured

scaly areas which burn and itch slightly. The rest of the hand is normal. During the extraction of teeth the first two fingers of the left hand are naturally within the mouth of the patient, while the right hand grasps the forceps. These two fingers are the ones which are involved, and it is fair to suppose that the condition on the two fingers of the left hand may be due to the procain oozing from the gums. He has never had procain injected for any purpose.

Skin Tests.—Skin tests were performed on the inner side of the left forearm with (1) sterile water; (2) a proprietary brand of procain; (3) procain (Metz), 2 per cent.; (4) procain, 1 per cent.; (5) cocain, 2 per cent, and (6) sterile water. He reported in twenty-four hours on the skin tests, stating that number 3 showed slight redness. In forty-eight hours examination revealed (1) no reaction; (2) an area of slight redness, about 5 mm. in diameter, very slightly elevated; (3) a red area, 6 to 7 mm. in diameter, redness most intense of all, with extension of redness in one direction for 1 cm.; slightly more elevation than in 2; (4) an area about 5 mm. in diameter, paler than 3, with extension in one direction for about 1 cm. The patient stated that redness and itching appeared on the day of examination; that he noticed nothing the day previous); (5) no reaction; (6) no reaction. The redness and slight itching persisted for ten days or two weeks.

SKIN TESTS

The skin tests in these cases were performed on the flexor surface of the forearm, the site of inoculation being produced by the twirling of a dental burr rather than by the use of a sharp-edged instrument. Sterile water was used as a control, and the various constituents of the procain solution and tablets were used in order to avoid the possibility of any interaction, and in order to test each substance separately. The reactions produced were observed for thirty minutes, after twenty-four hours, and again forty-eight hours after inoculation. A description of the results of these examinations has been given to aid in the interpretation.

The evidence offered by skin tests is debatable ground. In these three cases the evidence of these tests checks up with the clinical findings and is corroborated by the results of treatment. Further investigations are under way to find the number of persons sensitive to these various local anesthetics, and a report will be rendered at some later date. It is expecting too much to hope that the results will check as closely in all cases, and I feel that the final test, as Rackemann [2] says, is the agreement between the skin tests and the patient's history before making definite conclusions from the evidence of the skin tests.

SPECIFICITY OF REACTION

There are certain points in these cases which will bear additional emphasis. In all three cases an eruption appeared on the face, in

2. Rackemann, F. M.: The Clinical Study of One Hundred and Fifty Cases of Bronchial Asthma, Arch. Int. Med. **22**:517 (Oct.) 1918.

all probability associated with the accidental application of procain. This fact, with the evidence of the skin tests, indicates the specificity of the reaction to this particular drug and that it is a systemic condition, not merely a localized disturbance. In one case there is the possibility of a concomitant infection with a fungus. In this relation it is possible to suppose that the moist, soggy condition of the skin produced by the dermatitis would act as an excellent medium for the growth of these organisms which may be almost normal inhabitants of the skin. In only one case was there evidence of immediate allergic reaction, as evidenced by the appearance of wheals at the sites of inoculation; but all three cases showed evidences of specific reaction by papules and redness at the points of inoculation forty-eight hours afterward.

Here are three persons apparently susceptible to a drug which they have handled extensively, who have shown signs of a dermatitis on areas which this drug has reached, who have reacted to skin tests specifically for this particular drug, and whose condition has cleared up on refraining from the use of this particular agent. Several other cases have come to my attention, though not seen by me personally, in which dentists with an irritated condition of the hands while using procain, have experienced much improvement in their condition after using rubber gloves constantly while handling such solutions. It would seem then that sufficient evidence is presented to affirm that a susceptibility to procain has been the cause of dermatitis in this group. Moreover, the lapse of time from the beginning of the use of the drug to the onset of the irritation suggests that the susceptibility is acquired rather than hereditary.

ANAPHYLAXIS OR ALLERGY

The fact of this susceptibility brings up for consideration the phenomena of anaphylaxis or allergy. It is an open question whether these persons have become sensitized by the constant handling of procain and whether this dermatitis is an allergic reaction. An attempt was made to ascertain whether it was possible that these persons had become sensitized by the previous use of procain internally, that is, at previous extractions of teeth or previous operations. No history of subcutaneous use of procain was obtained. Highman and Michael,[3] in a recent paper, state that nothing is known of sensitization through normal integument, but that it is possible that the skin at these sites always presents microscopic injuries. In support of this they cite the case of an actor who developed angioneurotic edema following the application of grease paints, stating that this case may be a possible

3. Highman, W. J., and Michael, J. C.: Protein Sensitization in Skin Diseases: Urticaria and Its Allies, Arch. Dermat. & Syph. **2**:544 (Nov.) 1920.

example of parenteral sensitization. They also cite cases of guinea-pigs sensitized by inhaling sprayed foreign serum, and also call attention to the fact that sensitization through injured integument is conceivable because of the fact that extremely small amounts of alien protein may sensitize.

Can this drug act as an alien protein? It is known that other substances than proteins are able to produce reactions similar to those above described. The eruptive phenomena occurring occasionally after the administration of arsphenamin have been sufficiently impressed on our minds. Auer [4] states that the suggestion has been made that certain drug reactions may depend on the formation of compounds between the drug and the body proteins so that substances similar to foreign proteins are formed, and that this accounts for the resemblance to anaphylaxis which drug reactions may exhibit. This hypothesis, however, has not been established. In a summary of his experimental work along this line, he states that anaphylactic reaction may occur because the inflamed tissues are more active metabolically than normal tissues, and, therefore, the inflamed cells are affected by more antigen per unit of time than normal cells. Thus a lessened concentration of antigen for noninflamed sensitized cells may become effective when inflamed sensitized cells are concerned.

CHEMICAL EXPLANATION OF ANALOGOUS CONDITION

It is hardly possible at the present time to offer any explanation, even a partial one, on chemical grounds, but it is worth while to consider a somewhat analogous condition in rubber workers which has recently been described and explained on the basis of certain known chemical facts. The recent work of Shepard and Krall,[5] while not explaining the underlying cause of susceptibility, still makes an ingenious explanation of the causes of dermatitis associated with certain rubber workers. Their explanation is based sufficiently on known facts to make it appear plausible, and further investigation of causes along similar lines is justified from the work which they have performed. They report that certain of the workers in a rubber factory, which uses hexamethylenamin as an accelerator in the vulcanizing process, developed a dermatitis on forearms, arms and face, and were found to have a susceptibility to hexamethylenamin. They offer an explanation of the inflammatory process based on the fact that hexamethylenamin

4. Auer, John: Local Auto-Inoculation of the Sensitized Organism with Foreign Protein as a Cause of Abnormal Reactions, J. Exper. Med. **32**:427 (Oct.) 1920.

5. Shepard, N. A., and Krall, S.: Poisons in the Rubber Industry, The India Rubber World **61**:75 (Nov. 1) 1919.

is known to break down in the presence of acid and produce formaldehyd. The sweat is acid. The eruption is worse in hot weather. Formaldehyd alone does not produce a similar eruption. Formic acid does. They offer the explanation that possibly formaldehyd on the skin, in the hair follicles or glands, may be oxidized to formic acid, thus producing an irritation which is found in these workers. They offer as a solution to this condition the use of an alkaline solution. This treatment not only relieves the condition, but prevents its appearance, even in sensitized persons, when their hands and arms are immersed in the solution and allowed to dry before going to work. As I have said, no explanation is offered by these authors in regard to the underlying condition of susceptibility to hexamethylenamin, but the explanation of the cause of the dermatitis and its cure appears as a reasonable one.

POSSIBILITY OF GENERALIZED REACTIONS

It is interesting to conjecture as to the conditions which may be produced in persons susceptible to procain who subsequently receive injections for the extraction of teeth or for operative procedures. Do they have more local reaction, or do they have symptoms of a general nature? Dentists occasionally have patients who have become sick after a local anesthetic and may attribute that sickness to the excitement of the moment, to the actual extraction, possibly to sepsis afterward, or to the drug. There have not been, apparently, as many cases of illness produced after extraction of teeth since the use of procain, cocain apparently producing a greater effect on the person than the newer drugs. Three cases of death following procain have been found, one following extraction of teeth, and two following operative procedures on the antrum. All three of these were fairly sudden, and the case reports attribute these fatalities to the drug, although comment is made of the possibility that the operation and manipulation might have had some influence in the antrum cases.

The consideration of this subject of anaphylaxis in relation to dermatology by Highman and Michael, and Towle,[6] in recent papers, gives an accurate estimate of the current opinion in regard to this subject. This subject is, as they say, wholly on a theoretical basis as yet, but the fact remains that more and more cases and more and more diseases are being considered as candidates for admission to this particular group of dermatoses, and further study and analysis of these and other conditions will undoubtedly contribute much toward their eventual explanation.

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6. Towle, H. P.: Protein Sensitization in the Production of Skin Disease, Arch. Dermat. & Syph. **2**:531 (Nov.) 1920.

CONCLUSIONS

1. In dermatitis of the hands in dentists procain must be considered as a possible causal factor.

2. The clinical observations, together with the confirmatory results from skin tests, indicate an individual susceptibility.

3. The possibility of sensitization by means of the skin in these cases is suggested.

4. The treatment is obvious—to prevent the drug from reaching the hands, either by supporting its use, or by wearing rubber gloves.

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A FIFTH CASE OF SCLERODERMA WITH ARSENIC IN THE URINE

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LOS ANGELES

Scleroderma as a manifestation of chronic arsenic poisoning was discussed in a recent issue of THE ARCHIVES OF DERMATOLOGY AND SYPHILOGY.[1] Four consecutive cases were cited, three of the diffuse variety and one of the localized type, in which arsenic was demonstrated in the urine. The following is the fifth case of the series.

REPORT OF A CASE

History.—F. W. (No. 299872), in the outpatient department of the Massachusetts General Hospital, was a housewife of Russian Jewish extraction who had lived in Boston the past thirteen years. She was 34 years old, and up to the time of her present illness, which began four years ago, she had always enjoyed good health. Her husband and four children were living and well; there had been no miscarriages. She had never engaged in any occupation outside of her own housework, and so far as she knew, had never used any arsenical preparations or been exposed to arsenic in any form; she denied the use of any medicines prior to her present illness. Although she denied the use of any medicine containing arsenic during her illness, and although the hospital records show that none was used, the possibility of having received it from an outside source cannot be positively ruled out.

Neuritic Manifestations.—Neuritic manifestations ushered in the present illness. Numbness and soreness of the fingers of the right hand, and a few weeks later of the left hand, were the first symptoms noted. Since then there had been soreness, aching and attacks of cyanosis of the hands, legs and feet, especially during cold weather. During the first year the hands, forearms, legs and feet frequently became swollen after activity but improved following rest. Excessive perspiration of the palms had been constant. During the past year she had had difficulty in sleeping.

Skin.—The patient believed that the brown pigmentation and patches of leukoderma had been present about a year. She did not recall definitely when the skin began to harden, but the process had been progressive.

General Condition.—There had been weakness and great loss of weight. Occasional lacrimation had occured at night during the past year. There had been excessive flow of saliva at night during the past year, sufficient to wet the pillow. At intervals through the present illness, the tip of the tongue had been sore and burning, especially during cold weather. During the past four months she had had moderate sore throat. She had always had headaches which, during the present illness, had not been more severe than formerly.

Her appetite had been failing for the past two years. During the past eighteen months she had had attacks of pyrosis with eructations, relieved by

1. Ayres, Samuel, Jr.: Scleroderma as a Possible Manifestation of Chronic Arsenic Poisoning, Arch. Dermat. & Syph. **2**:747 (Dec.) 1920.

soda and to some extent by taking food; there had been no vomiting. During the past three weeks the bowels had moved three or four times a day, and there had been abdominal cramps like "knives going around," often severe enough to cause the patient to go to bed. There have been no bloody or tarry stools.

There have been no symptoms referable to the cardiorespiratory or genitourinary systems.

Examination.—The skin presented the most striking features. The areas of greatest involvement were the fingers, hands and forearms to just above the elbows. Here the skin was glossy, tightly drawn and infiltrated so that it could not be pinched up; the fingers were fixed in a claw-like flexion. These areas showed a brown pigmentation with a few patches of leukoderma. Both thighs were indurated but not pigmented. The lower two-thirds of the right leg showed pigmentation and sclero-edema; it pitted on pressure but the pitting remained a considerable length of time. The face was moderately involved; the pinnae of the ears were thickened, the nose was narrow and pointed with the skin drawn tight and the lips were narrow. Over the sternum the skin was infiltrated, and there were many telangiectases. The palms and soles were wet with perspiration, but there were no keratoses. Pubic hair was normal, but there was complete absence of axillary hair (the patient said she never had any). The scalp hair was of good quality but somewhat sparse; the eyelashes also were thin. The tongue was slightly coated in the center, but distinctly smooth and atrophic along the edges and tip. The tonsils were slightly large and red. The thyroid gland was not palpable; there were a few small palpable lymph glands in the neck. Knee jerks and plantar reflexes were absent; the pupils reacted to light. Sensation to pain and touch was normal. Both feet were flat. Aside from these findings, the physical examination was negative.

Laboratory Findings.—Routine blood and urine examinations were not made. The Wassermann reaction was negative. (Four years ago, at the beginning of her illness, the Wassermann reaction was reported positive at the Peter Bent Brigham Hospital, and she was given three intramuscular injections of mercury, but she failed to continue at the clinic; she received no arsenic there.) On August 19, a quart of urine was examined for arsenic by the Sanger method in the chemical laboratory of the hospital; no arsenic was found. On August 31, a second sample of urine and a specimen of hair were examined for arsenic, with negative results. The patient was then given a saturated solution of potassium iodid, ten drops three times a day; eighteen days later a third specimen of urine was tested, resulting in a definite positive qualitative test for arsenic. The presumption is that the potassium iodid combined with the arsenic, which was stored in the tissues, converting it into a soluble form which was easily eliminated, conforming to the reputation which potassium iodid enjoys in that respect. Putnam[2] has pointed out, however, that arsenic may be excreted only intermittently by the kidneys, and that even in acute fatal cases of arsenic poisoning the urine has been found free.

Recently Dr. Richard L. Sutton of Kansas City has added a sixth case to this series. His patient had the diffuse type of scleroderma and showed arsenic in the urine in an amount sufficient to quantitate. The test was made by the Kansas City Testing Laboratory. In neither of these two cases was the patient aware of the source of the arsenic.

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2. Putnam, J. J.: Boston M. & S. J. **122**:421, 1890.

It is desirable to emphasize strongly a point which was made in the previous paper on this subject, namely, that no assertion is being made that an etiologic relationship between scleroderma and chronic arsenic poisoning has been established. The evidence is entirely circumstantial, and the series of cases is too small to justify definite conclusions. However, the facts seem sufficiently interesting to warrant presentation merely for what they are worth.

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THE VALUE OF IODIN IN THE TREATMENT OF LEPROSY

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HONOLULU, H. I.

Potassium iodid, which has been used more or less extensively in the treatment of leprosy, especially during the period between 1860 and 1890, has been considered by most leprologists as harmful rather than helpful in the treatment of the disease. Danielson, who, during the earlier part of this period, probably experimented on a larger scale than any other authority was, however, satisfied that this drug was of great value, especially in the tubercular form of the disease. Having used potassium iodid personally, in a limited way, I became, early in my experience in the treatment of lepers, quite convinced that the so-called harmful action was, in fact, a curative one. Instead of giving the ordinary dose of 10 to 15 grains daily, I gradually increased the dose to between 100 and 200 grains. In one special case I gave even more than that amount daily for many days. The patients suffered greatly at times, especially those with the nerve type of leprosy affecting the median and ulnar nerves. Excruciating neuralgic pains along the nerves caused many sleepless nights, but those who persevered in the treatment were greatly benefitted. Large nodules would break down into open ulcers, and would finally heal with but little scar tissue, leaving not a single leper organism in the healed tissue. Beginning contracture of the hands would be abated, and often the condition of the hands returned to normal, sensation being completely restored.

When I became medical superintendent of the Kalihi Receiving Hospital for Lepers, situated in the outskirts of Honolulu, in January, 1910, I began giving iodin in the form of sajodin, a 32 per cent. iodin powder, the dose being gradually increased to 20 grains three times a day. I also employed iodin in the form of Lugol's solution in increasing doses to 20 drops three times a day. Later I commenced to use iodalbin, an iodin preparation containing about 22 per cent. of iodin. Of the three iodin preparations, I prefer iodalbin. Neither sajodin nor iodalbin in 20 grain doses would cause iodism or discomfort to the patient, while Lugol's solution, if continued, was liable to cause considerable irritation of the stomach. Improvement at first was extremely slow, but after the first six months curative results in some cases were quite rapid.

IODINIZED AUTOGENOUS SERUM

In association with this intensive use of iodin internally, I have attempted to use an iodinized autogenous serum obtained in the follow-

ing way: Skin lesions containing large numbers of lepra bacilli are frozen with a carbon dioxid snow pencil to produce a large bulla. The fluid from these bullae is withdrawn under antiseptic precautions and reinjected into the patient. Different lesions are used from time to time, but any single lesion is employed until the bacilli can no longer be obtained from it. This process is repeated at seven to ten day intervals. The basis for this therapeutic method is the belief that iodin, which passes out through all the secretions, would be contained in the serum, thus forming an iodinized autogenous serum. Furthermore, the increased blood supply brought to the part treated with the snow pencil would produce a local phagocytosis, and would aid in bringing the iodin directly in contact with the diseased tissue.

I am firmly convinced that this method of using iodin has a curative action in the treatment of leprosy. In my Board of Health Report dated June 30, 1913, I made the following statement: "My former experience with iodid of potassium in leprosy, and the more recent use of sajodin, leads me to the belief that if it were possible to form an iodin compound after the manner of the arsenical compound known as '606' wherein the iodin could with safety be exhibited intravenously, a marked specific for leprosy would be had." Janin, in 1913, reinjected serum from bullae with good results but did not use the snow pencil to make the bullae, or give iodin internally at the same time. In 1916, Hollman and Currie, using iodin hypodermically in combination with chaulmoogra oil, obtained good results. In 1919, Dean combined the derivatives of chaulmoogra oil—the fatty acid group first isolated by Rogers—with iodin, using a 2 per cent. iodin mixture hypodermically and a 5 per cent. iodin mixture internally, and gave added proof of the value of the iodin in the treatment of leprosy. I have frequently given iodin internally with the cacodylate of soda hypodermically, obtaining excellent results in selected types of incipient leprosy.

To obtain permanent curative results in leprosy it is just as essential to use iodin in combination with other recognized drugs as it is to use mercury and the iodids with arsphenamin in the treatment of syphilis. As in syphilis, it is self evident that the intensive treatment of leprosy should be carried out for at least three years, but in the latter the treatment should be strict hospitalization and supervision for an indefinite period.

ROENTGEN-RAY DOSAGE FROM THE PATHOLOGIC POINT OF VIEW

PRELIMINARY REPORT *

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NEW YORK

COMPARISON OF CELLS

Acute and subacute inflammatory tissues are characterized by lymphocytes—round cells. They are the least resistant of all pathologic cells and are the most readily influenced by therapeutic measures.

Chronic inflammatory tissues are characterized by fibroblasts—connective tissue cells. They are more resistant and less readily influenced than the lymphocytes.

Granulomas are characterized by giant, plasma and epithelioid cells. They are more resistant and less readily influenced than the inflammatory cells.

Neoplasm elements vary according to the type of tissue from which they originate. Those of the highest type (epithelial and glandular) are the most resistant and least readily influenced of all pathologic cells.

Normal tissue elements are more resistant than pathologic. The resistance varies according to the age of the person, the part of body and the type of tissue of which they are a part.

RESPONSE OF THE CELLS TO THE ACTION OF THE ROENTGEN-RAY

The intensity and the duration of the response of the cells to the roentgen-ray are in proportion to the degree of their resistance, that is, the response is most intense and of the longest duration in the cells of least resistance.

After a roentgen-ray exposure, the resistance of all cells is influenced and their activity is proportionately affected. The more resistant cells recover in less time than those of less resistance. If the interval between the exposures is sufficiently long, all the cells will recover. After a second exposure, the activity of the cells that have not fully recovered, is more readily affected as their resistance has already been influenced. With each successive exposure, the resistance is more and more influenced and the activity is proportionately less and less maintained. When the accumulative effects at the point of saturation are reached, the cells become nonresistant and inactive. The rapidity with which the point of saturation is reached depends on the character of

* From the Dermatological Department, Vanderbilt Clinic, New York.

the cells and the intensity of the exposures. It may result from a single exposure or from many exposures. When this stage is reached, involution sets in.

Involution.—The nonresistant and inactive tissue elements are unable to withstand the action of the local tissue assisted by the body's protective forces and are absorbed. (The body's protective forces are the circulating fluids and phagocytes.) If the involution is within bounds, normal absorption results. If it is rapid, ulceration may result. If normal tissue is involved, either ulceration or atrophy may result, depending on the rapidity of the absorption.

INTENSITY AND INTERVALS OF ROENTGEN-RAY EXPOSURES

Suberythema Doses.—Three weeks after a scalp is exposed to one unfiltered skin unit, the hair falls—an indication of complete inhibition of the hair papillae cells. As all the tissues exposed to the roentgen-ray are influenced, the pathologic cells, if exposed to suberythema doses, must be in the same state of inhibition at this time. Six weeks after the exposure the hair grows again—an indication of complete recovery of the hair papillae cells. As the intensity and the duration of the response to the roentgen ray are in proportion to the resistance, the pathologic cells will not have recovered to the same degree in the same time. If a second exposure is made at the time of recovery of the normal cells, that is, four weeks after the first exposure, the activity of the pathologic cells will be more affected, as their resistance has already been influenced.

Massive Doses.—About ten days after lesions are exposed to one and one-quarter to two and one-half skin units, an erythema develops in the surrounding area—an indication of complete inhibition of all the tissues exposed. About six weeks after the exposure the erythema completely disappears—an indication of complete recovery of the normal tissue elements. As normal tissue elements have greater resistance than pathologic and, as the intensity and duration of the response are in proportion to the resistance, the pathologic elements will not have recovered to the same degree in the same time. If a second exposure is made at this time, before the pathologic cells have completely recovered, their activity will be more affected as their resistance has already been influenced.

Summary.—The massive dose must not be repeated until the erythema has completely disappeared, which is an indication of normal tissue recovery. No tissue should be exposed to more than one skin unit in four weeks, the time of normal tissue recovery. If the exposures are repeated before the normal tissue elements have completely recovered, they may be so influenced that they will be absorbed, resulting in either ulceration or atrophy.

DOSAGE

Massive Doses.—One and one-fourth to two and one-half skin units should be given; this dose should be repeated when the erythema has completely disappeared.

TABLE 1.—RESPONSE IN CELLS OF LEAST RESISTANCE

Dose	Incomplete Recovery
Fractional doses, ¼ skin unit repeated every week	Acute and subacute inflammatory tissues.
Fractional doses, ½ skin unit, repeated every two weeks	Acute and subacute inflammatory tissues; chronic inflammatory tissues.
Suberythema doses, 1 skin unit, repeated every four weeks	Acute and subacute inflammatory tissues; chronic inflammatory tissues; granuloma.
Massive doses, 1¼ to 2½ skin units, repeated when erythema subsides	Acute and subacute inflammatory tissues; chronic inflammatory tissues; granuloma; neoplasm.

TABLE 2.—RESPONSE IN CELLS OF GREATEST RESISTANCE

Dose	Complete Recovery
Fractional doses, ¼ skin unit repeated every week	Normal; neoplasm; granuloma; chronic inflammatory tissues.
Fractional doses, ½ skin unit, repeated every two weeks	Normal; neoplasm; granuloma.
Suberythema doses, 1 skin unit, repeated every four weeks	Normal; neoplasm.
Massive doses, 1¼ to 2½ skin units, repeated when the erythema subsides	Normal.

Neoplasms, characterized by cells similar to those from which they originate, are exposed, according to their type, to a varying dose of from one and one-fourth to two and one-half skin units. After the erythema has subsided, usually in about six weeks, an involution of the lesion is sometimes noted. After repeated exposures, the involution is more marked and more rapid. The procedure is maintained until the lesions are entirely absorbed. An atrophy and sometimes telangiectasis are noted in the areas exposed. If the exposures are repeated before the erythema completely disappears, an ulceration may result. If exposed to one unit or less, the neoplasm cells recover during the intervals, and the new growth is not influenced.

Suberythema Doses.—Suberythema doses of one skin unit should be repeated every four weeks. Granulomas, characterized by cells less resistant than those of neoplasms, are exposed to one unit repeated every four weeks until complete involution results. If exposed to less than one unit, these cells recover and the lesions are not influenced.

Fractional Doses.—These consist of one-half skin unit repeated every two weeks. Chronic inflammatory tissues, characterized by cells

less resistant than those of granulomas, are exposed to half the dose in half the time, that is, one-half skin unit repeated every two weeks until complete involution results.

Fractional doses of one-fourth skin unit are repeated every week. Acute and subacute inflammatory tissues, characterized by cells of least resistance, are exposed to doses not exceeding one-quarter skin unit per week, repeated weekly until complete involution results.

The total amount of roentgen-ray for granulomas, acute, subacute and chronic inflammatory tissues, must not exceed one skin unit in four weeks. If exposed to larger doses, the response may be so active that ulceration may result.

Neoplasms and granulomas are seldom free from inflammatory tissue elements. If neoplasms are exposed to less than massive doses, and granulomas to less than suberythema doses, involution in these lesions is sometimes noted. The degree of involution depends on the amount of lymphoid or connective tissue elements present as part of, or about, these pathologic processes.

RESPONSE OF CELLS

The response is most intense and of longest duration in the cells of least resistance. These cells do not completely recover during the intervals between the exposures.

The response is least intense and of shortest duration in the cells of greatest resistance. These cells recover completely during the intervals between the exposures.

As it is never the agent but the response of the living cells to the agent that is responsible for the therapeutic results, the least amount of rays necessary to produce these results in any given tissue should be employed. If the dose is too intense, that is, the amount is excessive, the response may be so active that ulceration may result. If the amount is insufficient, the cells recover during the intervals, and the lesion is not influenced.

EXPERIMENTAL PRODUCTION OF CLINICAL TYPES OF SYPHILIS IN THE RABBIT*

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Syphilis in the human subject is characterized by the occurrence of a succession of lesions of various types which follow one another in a more or less orderly progression from the chancre to the terminal stages of the infection, and while to each period of the infection certain types of lesions have been assigned, the order of their appearance is not entirely fixed nor can one say just what lesions may be expected to occur in a given case.

The factors that determine these features of the disease may be numerous, and the results of their action differ so widely that diversity rather than uniformity has come to be recognized as one of the most fundamental characteristics of syphilis. The causes which underly this diversity of clinical types are but little understood. It is of course obvious that there are two sets of factors which may contribute to this condition, namely, the reactive mechanism of the host and the disease producing properties of the organisms concerned.

Within recent years, the tendency has been to lay more and more stress on the influence of the latter group of conditions. The possibilities of the existence of so-called strains of *Spirochaeta pallida* was first suggested by Noguchi [1] and later made the subject of experimental investigations by Nichols,[2] Reasoner [3] and others. More recently this idea has been emphasized by the work of Levaditi, Marie [4] and their co-workers in connection with general paresis. As yet, however, the subject of the cause of clinical variation is an open one, and while syphilographers have recognized the fact that many peculiarities of the infection may be due to causes other than strain differences, this possibility has been more or less neglected by experimental investigators.

It is not easy to approach the problem of clinical variation by means of observation on the human subject, since such a small part of the phenomena of infection can be observed in an individual case, and neither the host nor the causative agent is subject to the necessary

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* From the Laboratories of the Rockefeller Institute for Medical Research, New York.

1. Noguchi: J. Exper. Med. **15**:201, 1912.
2. Nichols: J. Exper. Med. **19**:362, 1914.
3. Reasoner: J. A. M. A. **67**:1799, 1916.
4. Levaditi and Marie: Ann. Int. Past. **33**:741, 1919. Marie, Levaditi and Banu: Compt. rend. Acad. d. Sc. **170**:1021, 1920.

measure of control. In the experimental animal, however, a large part of these difficulties are removable, and it is possible to reproduce many of the phenomena of the human infection under conditions of acceptable control. Thus by local inoculation into the testicles or scrotum of the rabbit, one may obtain an infection which begins with a primary lesion and after a lapse of from six to twelve weeks, is marked by the appearance of a variety of lesions in other parts of the body, together with a general lymphadenitis and at times by constitutional disturbances; there are lesions of the skin and appendages, the mucous membranes, the periosteum and bones, and of the eyes. The infection is not identical with that in man but the analogy is sufficiently close for one to make comparisons, and, at the same time, the differences are sufficiently great to enable one to make clear-cut experimental distinctions.

Variation in the clinical course of the disease is characteristic of the animal, as it is of the human, infection, and there are, as we have said, two aspects of the problem of variation, only one of which has been dealt with from an experimental standpoint. The subject of variation is an intricate one and at this time we do not propose to consider the ultimate possibilities of either of the potential factors concerned.

It has been noted, however, that with the use of a given strain of *Spirochaeta pallida,* one may still obtain infections which exhibit decided clinical variations, not only in the type of lesions which appeared in a given group of tissues, but equally so in the groups of tissues involved and this is of more fundamental importance. An analysis of the circumstances under which such variations occurred showed an appreciable connection between the experimental conditions employed and the type of infection produced. This was especially noticeable in the frequency with which keratitis and iritis occurred following the use of one set of conditions and the frequency with which lesions of the periosteum and bone followed another.

Previous experiments had shown that, while generalized lesions occurred in only a small percentage of rabbits inoculated by certain methods, it was possible to modify the course of the infection to such an extent that the occurrence of generalized lesions became the rule rather than the exception.[5] This work was founded on a modified conception of the theory of inhibition. That the development of a lesion in one testicle was capable of inhibiting the development of other lesions in the rabbit was first demonstrated by Nichols[6] in connection with metastatic lesions of the testicles and applied by him in

5. Brown and Pearce: Arch. Dermat. & Syph., 1920, **11**:675.
6. Nichols, H. J.: J. Exper. Med. **14**:211, 1911.

an explanation of the phenomena of relapse in human syphilis with especial reference to neurorecidives.[7]

Realizing the importance of the influence which the primary reaction exerted on the character of the infection in the rabbit, we were first able to convert a local into a general disease by diminishing or suppressing the testicular reaction. With a knowledge of what had been accomplished in this respect, it appeared that one might go a step further and, by modifying the defensive reaction in different ways, produce types of disease that would conform to alterations in the mechanism of animal resistance, the infecting organism being maintained as a constant factor in the reaction.

EXPERIMENTAL MODIFICATION OF THE INFECTION

Experiments that have been carried out show that definite type alterations can be produced in response to the use of experimental procedures which influence the reaction to infection. The character of the changes and the manner in which they were obtained may be illustrated by the following experiment:

Forty-four rabbits were inoculated in the testicles with the Nichols strain of *Spirochaeta pallida,* using for each testicle 0.5 c.c. of an emulsion containing numerous spirochetes, as many as four to eight to the microscopic field. The animals were divided equally into two series, A and B. Those of Series A were inoculated in both testicles and those of Series B in only one testicle. Lesions were palpable in the testicles at from ten to fourteen days after inoculation. Each series was then further divided into four groups, making each group as nearly comparable to the others of the series as possible from the standpoint of the animals and the state of the testicular infection. The several groups were handled as follows:

Group 1; Controls; Six Animals.—The infection in this group of animals was permitted to progress without interference of any kind.

Group 2; Early Castration; Five Animals.—These animals were castrated fourteen days after inoculation. In Series A, both testicles were removed; in Series B, only the infected testicle was removed.[8]

Group 3; Late Castration; Five Animals.—Castration was carried out as in Group 2, twenty-eight days after inoculaton.

Group 4; Therapeutic Suppression of Testicular Reaction; Six Animals.—These animals were given a single intravenous injection of arsenophenylglycyl dichloro-m-aminophenol for the purpose of temporarily suppressing the reaction in the testicle and of lowering the animal resistance.

All animals were kept under observation for from three to three and a half months after inoculation. During this time, they were examined almost daily and full records of the progress of the infection were kept.

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7. Nichols, H. J.: J. A. M. A. **63**:466, 1914.
8. All operations were done under ether anesthesia.

The purpose of some of these procedures may require a brief explanation. Early castration was employed as a means of aborting the testicular reaction early in the course of the infection and thus shifting the defensive reaction to other tissues before any considerable degree of protection had been developed. The use of late castration, on the other hand, represented an attempt to permit the infection to progress to a point at which the protection developing from the primary foci was nearly, but not quite, sufficient to prevent the occurrence of lesions in other parts of the body. The success of this attempt hinged on the judgment of the proper time at which to intervene, and castration was performed as the first cycle of testicular reaction was nearing completion. The progress of the infection was, of course, not uniform in all animals, and the time fixed for castration was based on the average animal of the group; this was too early in some cases and too late in others, but such irregularities could not be avoided if a constant time element were to be maintained.

The use of a therapeutic agent in this series of experiments was intended to accomplish more than a temporary restraint on the primary lesions. The effects produced by such agents are not entirely measurable by the reduction which they produce in existing lesions and, while we cannot discuss the action of therapeutic agents, it is necessary to state that in addition to any effect which may be attributable to a temporary suppression of existing lesions, therapeutic agents frequently nullify any protection that has been developed and render subsequent reactions on the part of the animal less effectual. It was for this purpose that arsenophenylglycyl dichloro-m-aminophenol was used.

The period of observation chosen was fixed with a view to including only one cycle of general reaction. Clinical relapse is prone to occur in the animal as in the human subject, and the inclusion of this class of phenomena would introduce more complex elements, which cannot be considered in this article.

RESULTS OBTAINED

The influence which these procedures exerted on the course and character of the infection may be learned from a comparison of the case incidence and relative severity of generalized lesions, the groups of tissues involved, the order of involvement and the time after inoculation at which the lesions appeared. For convenience, these facts have been tabulated in parallel columns in the table. The list of conditions given includes no lesions of uncertain or doubtful character. When any doubt existed, the condition was recorded as suspicious or doubtful, as the case might be, and animals showing such affections are marked with an asterisk (*).

As one examines the data recorded in the table, the first thing to be noted is that the occurrence and the severity of generalized lesions among animals of a given group was inconstant. This indicates the existence of a variable in the reaction of individual animals to a given set of conditions which must be regarded as present in all cases.

EFFECT PRODUCED ON THE CHARACTER OF THE INFECTION BY MODIFYING THE REACTION OF THE HOST IN ANIMALS INOCULATED WITH A CONSTANT DOSE OF A GIVEN STRAIN OF SPIROCHAETA PALLIDA

Series A: Bilateral Inoculations			Series B: Unilateral Inoculations		
Number and Group	Generalized Syphilis	Lesions in Order of Their Appearance, Time in Days	Number and Group	Generalized Syphilis	Lesions in Order of Their Appearance, Time in Days
Group 1A			Group 1B		
1	—*		1	—*	
2	—		2	++	S.(57,78) E.(78)
3	—		3	—*	
4	—*		4	++	P.B.(55) E.(78,84)
5	—		5	—	
6	+	S.(57)	6	++++	S.(57,71) P.B.(63)
Group 2A			Group 2B†		
1	—*		1	++	P.B.(50)
2	++	S.(28) MM.(41)	2	++	MM.(41) P.B.(73,78)
3	—		3	+	P.B.(57)
4	++	P.B.(79) S.(89)	4	++	P.B.(41,57) S.(57)
5	+++	P.B.(57,78) S.(79) E.(85)			
Group 3A			Group 3B†		
1	++	P.B.(57) S.(71)	1	+	MM.(63)
2	—*		2	—	
3	+++	S.(29) MM.(63) E.(80,84)	3	+++	P.B.(50) S.(50,76)
4	+	E.(85)	4	—*	
5	++	S.(50) E.(65)			
Group 4A			Group 4B		
1	+	P.B.(63) S.(71,78,80)	1	++	P.B.(55) S.(90)
2	+	P.B.(57)	2	+++	P.B.(55,57)
3	—*		3‡	+	P.B.(47)
4	+++	P.B.(50) S.(50,57) MM.(71)	4	++	P.B.(55) E.(97)
5	++	P.B.(41)	5	++	S.(35) P.B.(59)
6	++	P.B.(71,78)	6	++	S.(63) MM.(97)

— Negative
\+ Slight infection
++ Moderate infection
+++ Well marked infection
++++ Extremely marked infection

E., eyes; MM., mucous membranes and mucocutaneous borders; P.B., periosteum and bone; S., skin.

* Animals showing suspicious lesions, not definite.

† One animal in each of these groups died before results could be determined.

‡ The animal developed symptoms of acute meningitis as the first lesions were appearing and was anesthetized and killed. Spirochetes were recovered from the cerebrospinal fluid. There was no bacterial infection.

Figures in parentheses ( ) give the time in days in which the lesions appeared.

Considering the character of the infection which occurred under the several conditions employed, it will be seen that it varied from an infection in which scarcely any lesions were demonstrable (except those in the testicles), as in Group 1 A, to infections in which a variety of generalized lesions occurred in practically all the animals of the group. This is the first respect in which it can be seen that a modification in the type of the infection was produced.

The next condition to be noted is that the character of the disease among the animals of a given group also varied. In Group 1 B, for example, there was one case of skin and eye infection, another of bone and eye infection and a third of skin and bone infection; or, there were two cases each of skin, bone and eye infection. A similar condition prevailed in Group 2 A but in 2 B a different type of result was obtained. Here there was an unbroken series of cases of bone syphilis, two of the four animals showing skin or mucous lesions as well.

That the occurrence of such a group of infections cannot be regarded as a coincidence is shown by the fact that when analogous conditions were employed in Groups 4 A and B, the same type of infection was again produced. Further than this, a distinctly different type of infection was produced in the animals of Group 3 A by permitting the testicular reaction to progress much longer before suppression was attempted. In only one of the four animals in this group did bone lesions occur as contrasted with its occurrence in all of those of Groups 2 B and 4 A, and five of the six animals in 4 B. The infection in Group 3 A was preeminently one of skin and eyes; three of the animals showed skin lesions and three of them eye lesions and in one the eye lesions were the only lesions present.

The prominence of the latter type of infection is not fully brought out in this series of experiments, which covered only a little more than three months. This, as we realized, did not afford a proper opportunity for the development of eye lesions, which are rarely seen until toward the end of the third month and which tend to occur later when other conditions are most marked. Skin lesions showed the same tendency to late appearance under similar circumstances, and late lesions would doubtless have been more numerous had the period of observation been longer. The occurrence of these late lesions would not have altered the general type of the infection, however, but would merely have served to emphasize the conditions described.

In contrasting the manifestations of syphilis in the rabbit with those of man, attention should be called to two conditions: First, that the disease in the rabbit is not entirely comparable either to the acquired or the congenital form of the human infection, but presents an interesting combination of the two conditions. In the second place, the most noticeable difference in the sequence of tissue involvement is the position occupied by skin and bone infections, which is the reverse of that in man (acquired syphilis). This is to be accounted for by the fact that in the rabbit the skin is a furred coat, and for the most part, is less subject to infection or to the action of a host of conditions which predispose to skin infection than is the skin of man.

CLINICAL TYPES OF DISEASE

The fact that it is possible to produce a scale of variations in the clinical course of syphilitic infections by modifying the reaction of the experimental animal, indicates the importance of this group of factors in determining the character of the disease. It also suggests that each group of tissue reactions, or lesions, bears some relation to the reactions or lesions of other tissues and, therefore, to the course of the disease as a whole.

We shall not attempt to give a detailed statement of these relationships, but the simplest explanation which can be offered for the results reported is one which is based on inherent tissue susceptibility and tissue reactivity.

In the first place, the occurrence or nonoccurrence of generalized lesions in the rabbit, as well as the character of these lesions, appears to depend primarily on a protective reaction which takes place at the primary foci of infection and to some extent on the relative susceptibility of other tissues. It is difficult to say what part the latter condition plays in determining the general course of the disease, but unless a given tissue furnishes suitable conditions for the growth and multiplication of the spirochetes, no very active lesions are likely to occur, nor will the reaction in such tissues contribute materially to the defensive mechanism either locally or generally.

In the second place, it is conceivable that the protection developed from a given source may not affect all tissues, or even all parts of the body, in an equal degree or at the same rate, but that it may be extended progressively from the primary lesions to successive tissue groups, being sufficient to protect one group of tissues at a time when little or no protection is afforded to another.

According to this conception, the tissues which become involved or the lesions which develop in any given case would represent a measure of the effectiveness and the state or progress of the reaction in that animal. That such may be the case is indicated by the fact that certain groups of tissues tend to become involved in a given order; thus, bone lesions, if they occur at all, tend to follow those of the testicles or scrotum, while keratitis and iritis occur toward the end of the cycle of tissue involvement, the skin and mucous membranes occupying an intermediate position. Further than this, it has been shown that by early and radical interference, it is possible to so alter the course of the disease as to cause bone lesions practically to supplant those of the testicle in the defensive reaction; conversely, by permitting the testicular reaction to progress to a given point, it is possible to confer protection on this group of structures. In this case no bone lesions occur, but the generalized disease begins with involvement of the next group of tissues in order, producing an infection which is essentially one of the skin, mucous membranes and eyes.

Going still further, it is found that while, in the majority of animals inoculated in both testicles a high degree of protection seems to be conferred on other tissues of the body, in many instances, the protection fails to reach the eyes, lesions of the cornea and iris appear as the only clinical manifestations of a generalized disease.

This fact, taken in conjunction with other circumstances surrounding eye infections, is of especial interest on account of a point of view which is introduced toward certain manifestations of syphilis, especially neurosyphilis. In the rabbit, eye lesions are not only terminal and frequently the only generalized conditions that occur, but they are also relatively slight and more prone to repeated relapse than any other class of lesions. In the light of the conditions reported in the foregoing, these circumstances suggest that all tissues are not equally protected by the general reaction which occurs during the early stages of a syphilitic infection and that certain tissues which fail to receive this protection, although less susceptible to injury or infection than other tissues, may be capable of only a relatively slight degree of self-protection. This is undoubtedly the case in the experimental animal, and if similar conditions obtain in man, such conditions as neurosyphilis may be explainable on this basis.

It was the peculiar chain of circumstances surrounding eye infections which first drew our attention to the possibilty of establishing the existence of a definite sequence of defensive reactions in the experimental animal with its corollary of a sequence in tissue protection and the possibility of producing infections of different types by modifying the defensive reaction at its source. The type of infection produced, therefore, by the inoculation of a given strain of *Spirochaeta pallida*, may be regarded as a resultant of the operation of the several factors indicated and subject, through this cause alone, to a wide degree of variation.

SUMMARY AND CONCLUSIONS

In the course of investigations dealing with generalized syphilis in the rabbit, it was noted that distinctly different types of disease were frequently produced by inoculations made with a given strain of *Spirochaeta pallida;* it also appeared that there was an appreciable connection between the experimental conditions employed and the type of disease which occurred.

Since it had been found possible to convert a disease which is usually localized into a generalized disease by diminishing or suppressing the primary reaction, it appeared that by modiying the reaction in different ways, one might produce types of disease which would conform to alterations in the defensive mechanism. Experiments carried out on a large series of animals showed that such was the case. By various

experimental procedures, different types of infection were produced, and in this way it was found that there was a definite sequence of tissue involvement or of tissue reactions which made it possible to produce infection or to confer protection on a given group of tissues according to the nature of the means employed.

From the manner in which the infection responded to modifications of the defensive reaction, the conclusion was drawn that a wide variation in the clinical type of the disease might be traceable to this one group of causes. This, of course, does not eliminate the possibilty that variation in the biologic properties of the infecting organisms may contribute to further variations in the type of the disease.

A STUDY OF ARSPHENAMIN–SERUM PRECIPITATES AND THEIR RELATION TO CLINICAL REACTIONS *

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Of the numerous theories advanced in explanation of the reactions and fatalities following the intravenous injection of solutions of arsphenamin, considerable attention has been given to those based on the formation of precipitates in the blood which may result in pulmonary embolism and the production of immediate symptoms and even death.

REVIEW OF LITERATURE

As early as 1911, Michaelis [1] suggested that precipitates found in the blood in vivo may be responsible for fatalities following the intravenous injection of arsphenamin and a little later Miessner [2] showed that mixtures of acid solutions of arsphenamin and defibrinated blood or horse serum in test tubes produced heavy precipitates. When an alkaline solution of arsphenamin was used, he failed to obtain these precipitates. Schottmüller [3] reported the same results from mixtures in vitro of acid and of alkaline solutions of arsphenamin and blood plasma. Both Miessner and Schottmüller suggested that these precipitates may have been the cause of death in certain instances following the intravenous injection of acid solutions of arsphenamin. In an extensive series of experiments with rabbits and dogs, Joseph [4] corroborated Miessner's observations that acid but not alkaline solutions produced precipitates when mixed with blood in test tubes, and that the intravenous injection of acid solutions produced precipitates in the venous blood which collected in the right side of the heart and in the lungs.

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* From the Dermatological Laboratories of Philadelphia.

* This investigation was aided by funds accruing from the preparation of arsphenamin.

1. Michaelis, L.: Die Ehrlich-Hata Behandlung in der inneren Medizin. Deutsch. med. Wchnschr. **36**:2278, 1910.

2. Miessner: Die Ursache für die giftige Wirkung saurer Salvarsanlosungen. Deutsch. med. Wchnschr. **37**:491, 1911.

3. Schottmüller: Deutsch. med. Wchnschr. **37**:670, 1911.

4. Joseph, D. R.: On the Formation of Precipitates After the Intravenous Injection of Salvarsan, J. Exper. Med. **14**:83, 1911.

The composition of these precipitates has also been a subject of much interest; Fleig [5] regarded them as precipitated proteins, while Danysz,[6] who more recently has expounded these theories of precipitation, believes that the precipitates are largely composed of the insoluble arsphenamin base or insoluble compounds of the base in combination with calcium phosphates.

Berman [7] regards the precipitates as composed of proteins and suggests that an increased protein content of the blood in certain syphilitic patients may favor precipitation in vivo, even of properly alkalinized solutions of arsphenamin. Berman analyzed the blood of two patients by the nephlometric method of Kober and Graves and found an increased protein content, essentially of the globulins. Furthermore, the serums of eleven patients, among 300 injections, who developed an immediate reaction following the intravenous injection of alkaline solutions of arsphenamin, produced heavy whitish yellow precipitates when mixed in test tubes with the arsphenamin solutions, whereas the serums of nonreacting subjects, according to Berman, did not. Berman states that by previously testing the serum and the solution of arsphenamin one could tell whether or not an immediate reaction (designated as the "nitritoid crisis") would follow the injection.

The investigations of Schamberg, Kolmer, Raiziss and Weiss [8] essentially confirmed the observations of Miessner and Joseph that precipitates are produced only when acid or insufficiently neutralized solutions of arsphenamin are added to serum, plasma or defibrinated blood. Furthermore, they showed that solutions of neo-arsphenamin do not produce these precipitates but may nevertheless produce immediate reactions similar to those produced by arsphenamin when administered to human beings by intravenous injection. The precipitates formed in mixtures of blood and acid solutions of arsphenamin were found to be composed of arsphenamin which immediately dissolved on the addition of a weak alkali, such as decinormal solutions of sodium hydroxid.

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5. Fleig, C.: La toxicite de la salvarsan (Monograph), Paris, 1914.

6. Danysz, J.: Les proprietes physicochemiques des produits du groupe des arsenobenzenes leurs transformations dans l'organisme, Ann. d. l'Inst. Pasteur **31**:114, 1917.

7. Berman, L.: The Nitritoid Crises After Arsphenamin Injections, Arch. Int. Med. **22**:217, 1918.

8. Schamberg, J. F.; Kolmer, J. A.; Raiziss, G. W., and Weiss, C.: Laboratory and Clinical Studies Bearing on the Causes of the Reactions Following Intravenous Injections of Arsphenamin and Neo-Arsphenamin, Arch. Dermat. & Syph. **1**:235, 1920.

PURPOSES OF INVESTIGATION

The chief purpose of this investigation has been to study the serums, by Berman's technic, of those persons showing reactions while being treated for syphilis with intravenous injections of arsphenamin and neo-arsphenamin.

Berman's work was based on a study of the serums of eleven persons who showed a reaction (designated by Milian as the "nitritoid crisis) during, or immediately after, the intravenous injection of arsphenamin and characterized by redness of the face, dyspnea, a feeling of anguish and distress, cough and precordial pain. Our investigation has included a study of the serums, not only of patients showing these immediate reactions, but likewise the serums of patients showing the symptoms of early reactions, as designated by Schamberg, Kolmer and Raiziss,[9] and characterized by chilliness or a distinct rigor, headache, vertigo, nausea, vomiting, diarrhea and rise of temperature developing within an hour or two or any time within twenty-four hours, after the intravenous injection of arsphenamin or neo-arsphenamin.

In this investigation we have confined ourselves to a study of the reactions described by Berman following the mixing of serums and solutions of arsphenamin in test tubes in relation to the clinical reaction; special studies on the proteins of the serums of syphilitic patients have been made by one of us (Tokuda), employing a refractometric method, the results being given in a separate communication.

TECHNIC

Blood was collected from a series of patients before the intravenous injections of arsphenamin or neo-arsphenamin were made, and the serums were tested with monosodium and disodium solutions of arsphenamin and solutions of neo-arsphenamin. Acid solutions of arsphenamin were not employed because every serum shows a heavy precipitate when mixed with these.

The solutions of arsphenamin used in the tests were 2 per cent. and of neo-arsphenamin 4 per cent. The monosodium solutions of arsphenamin were prepared by adding just enough sodium hydroxid to "clear" the solution after the precipitate had formed; the disodium solutions were prepared by adding one third excess of alkali after the solution had been "cleared."

The tests were conducted by placing 0.5 c.c. fresh unheated serum in three small test tubes and adding 0.5 c.c. of the monosodium and disodium solutions of arsphenamin and the solution of neo-arsphenamin

9. Schamberg, J. F.; Kolmer, J. A., and Raiziss, G. W.: Experimental and Clinical Studies of the Toxicity of Dioxydiamino-Arsenobenzene Dichlorhydrate, J. Cutan. Dis. **35**:286, (May-June) 1917.

to numbers 1, 2 and 3, respectively; controls were included in each set of tests in which saline solution replaced serum. The reactions were read at once and again one hour after standing at room temperature and recorded thus: — indicates that the mixtures remained clear; + indicates that the mixtures became opalescent; ++ indicates that the mixtures became turbid, and +++ indicates that the mixtures became turbid with the production of a whitish yellow precipitate.

The patients were given intravenous injections of monosodium arsphenamin (just enough alkali to clear the solution), each 0.1 gm. being dissolved in about 20 c.c. of whitish water. The neo-arsphenamin was administered in dilute solutions and also in concentrated solutions by means of a syringe.

The "immediate reactions" referred to were observed in the clinic during, or immediately after, the injections. For the "early reactions" we were obliged to accept the statements of patients who left the clinic without symptoms but reported on furnished blanks the subsequently developing symptoms previously mentioned and classified under the "early reaction."

RESULTS

The results are summarized in Tables 1, 2, 3, 4 and 5.

While this study was being made no "immediate reactions" or "nitritoid crises" were observed during the administration of arsphenamin, but sixteen patients developed these reactions during the administration of neo-arsphenamin. The serum reactions are shown in Table 1.

TABLE 1. — RESULTS WITH THE SERUMS OF SIXTEEN PATIENTS SHOWING IMMEDIATE REACTIONS DURING THE INTRAVENOUS INJECTION OF NEO-ARSPHENAMIN

Compound Administered	Serum Reactions With Monosodium Arsphenamin		Serum Reactions With Disodium Arsphenamin		Serum Reactions With Neo-arsphenamin	
	At Once	After One Hour	At Once	After One Hour	At Once	After One Hour
No. 498	—*	++	—	—	—	—
No. 498	—	++	—	—	—	+
No. 518	++	++	—	+	—	+
No. 506	++	++	—	—	—	—
No. 544	—	—	—	—	—	—
No. 566	—	—	—	—	—	—
No. 541	—	—	—	—	—	—
No. 585	+	+++	—	—	—	—
No. 585	—	—	—	—	—	+
No. 589	—	—	—	—	—	—
No. 620	—	—	—	—	—	+
No. 641	—	—	—	—	—	—
No. 641	—	—	—	—	—	—
No. 654	—	—	—	—	—	—
No. 667	—	—	—	—	—	—
No. 651	—	—	—	—	—	+

* — indicates that mixtures of serum and arsphenamin solution were perfectly clear; +, opalescent; ++, turbid; +++, very turbid with precipitate.

Ten patients developed "early reactions" following the intravenous injection of arsphenamin. The serum reactions are given in Table 2.

TABLE 2.—RESULTS WITH THE SERUMS OF TEN PATIENTS SHOWING EARLY REACTIONS FOLLOWING THE INTRAVENOUS INJECTION OF ARSPHENAMIN

Compound Administered	Serum Reactions With Monosodium Arsphenamin		Serum Reactions With Disodium Arsphenamin		Serum Reactions With Neo-arsphenamin	
	At Once	After One Hour	At Once	After One Hour	At Once	After One Hour
No. 3586	—*	—	0	0	0	0
No. 3586	—	—	—	—	—	—
No. 3592	—	++	—	—	—	—
No. 3592	—	++	—	—	—	—
No. 3592	—	—	—	—	—	—
No. 3592	—	—	—	—	—	—
No. 3592	—	—	—	—	—	—
No. 3605	—	++	—	—	—	—
No. 3605	—	++	—	—	—	—
No. 3605	—	++	—	—	—	—

* — indicates that mixtures of serum and arsphenamin solution were perfectly clear; +, opalescent; ++, turbid.

Twenty-five patients developed "early reactions" following the intravenous injection of neo-arsphenamin. The serum reactions are given in Table 3.

TABLE 3.—RESULTS WITH THE SERUMS OF TWENTY-FIVE PATIENTS SHOWING EARLY REACTIONS FOLLOWING THE INTRAVENOUS INJECTION OF NEO-ARSPHENAMIN

Compound Administered	Serum Reactions With Monosodium Arsphenamin		Serum Reactions With Disodium Arsphenamin		Serum Reactions With Neo-arsphenamin	
	At Once	After One Hour	At Once	After One Hour	At Once	After One Hour
No. 487	—*	—	0	0	0	0
No. 487	—	—	—	—	—	—
No. 468	—	—	—	—	—	—
No. 498	—	++	—	—	—	—
No. 518	—	+	—	—	—	—
No. 499	—	+	—	—	—	—
No. 499	—	++	—	—	—	—
No. 509	—	++	—	—	—	—
No. 509	—	++	—	—	—	—
No. 519	—	+	—	—	—	—
No. 521	—	+	—	—	—	—
No. 497	+	++	—	—	—	—
No. 518	+	++	—	—	—	—
No. 526	+	++	—	—	—	—
No. 526	+	++	—	—	—	—
No. 533	—	+	—	—	—	—
No. 533	+	++	—	—	—	—
No. 544	+	++	—	—	—	—
No. 544	+	++	—	—	—	—
No. 533	+	++	—	—	—	—
No. 538	+	++	—	—	—	—
No. 547	+	++	—	—	—	—
No. 558	+	++	—	—	—	—
No. 544	—	—	—	—	—	—
No. 574	—	—	—	—	—	—

* — indicates that mixtures of serum and arsphenamin solution were perfectly clear; +, opalescent; ++, turbid.

Table 4 gives the serum reactions of twenty-five patients who did not show any symptoms of reactions after the intravenous injection of arsphenamin; Table 5 gives the serum reactions of sixty-six patients who did not show any symptoms after the administration of neo-arsphenamin. Both tables are introduced as controls.

TABLE 4.—Results with the Serums of Twenty-Five Patients Who Did Not Show Any Reactions After the Administration of Arsphenamin

Compound Administered	Serum Reactions With Monosodium Arsphenamin		Serum Reactions With Disodium Arsphenamin		Serum Reactions With Neo-arsphenamin	
	At Once	After One Hour	At Once	After One Hour	At Once	After One Hour
No. 3570	—*	—	—	—	—	—
No. 3570	—	—	—	—	—	—
No. 3570	—	—	—	—	—	—
No. 3570	—	—	—	—	—	—
No. 3570	—	—	—	—	—	—
No. 3586	+	++	—	—	—	—
No. 3586	+	++	—	—	—	—
No. 3586	+	++	—	—	—	—
No. 3586	+	++	—	—	—	—
No. 3570	—	+	—	—	—	—
No. 3570	—	++	—	—	—	—
No. 3570	—	+	—	—	—	—
No. 3570	—	+	—	—	—	—
No. 3592	—	++	—	—	—	—
No. 3592	—	++	—	—	—	—
No. 3592	—	++	—	—	—	—
No. 3592	—	—	—	—	—	—
No. 3605	—	+	—	—	—	—
No. 3605	—	+	—	—	—	—
No. 3605	—	+	—	—	—	—
No. 3605	+	++	—	—	—	—
No. 3605	+	++	—	—	—	—
No. 3605	+	++	—	—	—	—
No. 3530	—	+	—	—	—	—
No. 3530	—	+	—	—	—	—

* — indicates that mixtures of serum and arsphenamin solution were perfectly clear; +, opalescent; ++, turbid.

These results are summarized in Table 6 which shows at a glance the percentages of positive serum reactions with the different solutions of arsphenamin and neo-arsphenamin. In preparing this table, only ++ and +++ reactions developing at once with the solutions of arsphenamin have been included as possibly possessing some significance and corresponding to the reactions described by Berman. As stated by Berman, + reactions (opalescence) may be excluded. Reactions developing after the mixtures have stood one hour are likewise of little significance as this phenomenon has been found so frequently with normal serums and the serums of lower animals.

Since mixtures of solutions of neo-arsphenamin and serum are usually perfectly clear even after standing one hour, positive reactions may be of some significance and are included.

TABLE 5.—Results with the Serums of Sixty-Six Patients Who Did Not Show Any Reactions After the Administration of Neo-Arsphenamin

Compound Administered	Serum Reactions With Monosodium Arsphenamin		Serum Reactions With Disodium Arsphenamin		Serum Reactions With Neo-arsphenamin	
	At Once	After One Hour	At Once	After One Hour	At Once	After One Hour
No. 487	—*	—	—	—	—	—
No. 487	—	—	—	—	—	—
No. 487	—	—	—	—	—	—
No. 487	—	—	—	—	—	—
No. 468	—	—	—	—	—	—
No. 468	—	—	—	—	—	—
No. 487	—	—	—	—	—	—
No. 484	+	++	—	—	—	—
No. 484	++	++	—	—	—	—
No. 484	++	++	—	—	—	—
No. 484	+	++	—	—	—	—
No. 484	+	++	—	—	—	—
No. 465	+	++	—	—	—	—
No. 465	+	++	—	—	—	—
No. 459	—	+	—	—	—	—
No. 459	—	+	—	—	—	—
No. 503	—	++	—	—	—	—
No. 493	—	++	—	—	—	—
No. 506	—	+	—	—	—	—
No. 509	—	+	—	—	—	—
No. 512	—	+	—	—	—	—
No. 518	—	+	—	—	—	—
No. 518	—	+	—	—	—	—
No. 518	—	+	—	—	—	—
No. 499	—	+	—	—	—	—
No. 353	—	+	—	—	—	—
No. 509	—	+	—	—	—	—
No. 509	—	+	—	—	—	—
No. 521	—	+	—	—	—	—
No. 521	—	+	—	—	—	—
No. 518	++	++	—	—	—	—
No. 506	++	++	—	—	—	—
No. 526	—	+	—	—	—	—
No. 529	—	+	—	—	—	—
No. 529	—	+	—	—	—	—
No. 533	—	+	—	—	—	—
No. 533	—	+	—	—	—	—
No. 533	—	++	—	—	—	—
No. 533	—	+	—	—	—	—
No. 533	—	++	—	—	—	—
No. 533	—	—	—	—	—	—
No. 538	—	+	—	—	—	—
No. 538	—	+	—	—	—	—
No. 538	—	+	—	—	—	—
No. 523	—	++	—	—	—	—
No. 554	+	++	—	—	—	—
No. 554	+	++	—	—	—	—
No. 554	+	++	—	—	—	—
No. 538	+	++	—	—	—	—
No. 538	+	++	—	—	—	—
No. 544	+	++	—	—	—	—
No. 544	++	++	—	—	—	—
No. 558	++	++	—	—	—	—
No. 547	++	++	—	—	—	—
No. 547	+	++	—	—	—	—
No. 547	+	++	—	—	—	—
No. 541	+	++	—	—	—	—
No. 541	+	++	—	—	—	—
No. 562	—	+	—	—	—	—
No. 533	—	+	—	—	—	—
No. 544	—	—	—	—	—	—
No. 550	—	—	—	—	—	—
No. 550	—	+	—	—	—	—
No. 570	—	—	—	—	—	—
No. 566	—	—	—	—	—	—
No. 574	—	—	—	—	—	—

* — indicates that mixtures of serum and arsphenamin solution were perfectly clear; +, opalescent; ++, turbid.

TABLE 6.—Summary Showing Percentages of Serums Yielding Turbid Reactions at Once When Mixed with Solutions of Arsphenamin and Opalescent Reactions within One Hour When Mixed with Solutions of Neo-Arsphenamin

Reactions	Number Tested	Percentages of Positive Serum Reactions With		
		Monosodium Arsphenamin	Disodium Arsphenamin	Neo-arsphenamin
Immediate reactions after neo-arsphenamin	16	12	—	31
Early reactions after arsphenamin	10	—	—	—
Early reactions after neo-arsphenamin	25	—	—	—
No reactions after arsphenamin	25	—	—	—
No reactions after neo-arsphenamin	66	11	—	5

SUMMARY

1. The amount of alkali in the solutions of arsphenamin has great influence on the reactions following the mixture of a serum and arsphenamin in test tubes. For this reason the solutions of monosodium arsphenamin produce more precipitates than the disodium solutions because the latter contain an excess of alkali. Furthermore, all precipitates, including those produced when acid solutions of arsphenamin are mixed with serums, can be dissolved at once by the addition of a few drops of a normal solution of sodium hydroxid. This constitutes proof that the precipitate is a drug precipitate and not a protein precipitate, because a protein precipitate could not be redissolved in this manner.

2. The amount of alkali in the solutions of neo-arsphenamin may have a similar relation to the results observed when solutions are mixed with serums. The results observed in these experiments indicated that the solution of some lots of neo-arsphenamin produced more positive reactions than other lots; furthermore, the addition of a single drop of normal sodium hydroxid immediately dissolved the precipitates and yielded clear solutions.

3. The serums of patients exhibiting immediate (nitritoid) reactions after neo-arsphenamin did not form precipitates when brought in contact, in the test tube, with solutions of neo-arsphenamin. Negative results were similarly obtained with the serums of patients who had febrile and gastro-intestinal reactions.

4. Test tube precipitates of arsphenamin occurred as frequently and as pronouncedly with the serums of patients not exhibiting febrile and gastro-intestinal reactions after arsphenamin as with the serums of those who did manifest such reactions. As practically no nitritoid reactions occurred after arsphenamin during the period of our study, the serums of such patients could not be tested.

5. In so far as the results observed with the serums of patients showing immediate (nitritoid) reactions after the administration of neo-arsphenamin are concerned, we found no evidence to support the deductions of Berman that these simple tests will serve to foretell the occurrence of these reactions, although it must be stated that Berman's tests were conducted with the serums of patients who had "nitritoid" reactions after the administration of arsphenamin.

6. It is highly probable that the reactions observed when serums and solutions of arsphenamin and neo-arsphenamin are mixed in test tubes, are primarily dependent on the amount of alkali present in the solutions or in the serums. The amount of alkali present in different lots of arsphenamin and neo-arsphenamin is likely to vary and thereby influence the occurrence of precipitates with different lots of the drugs and the serums of patients. These precipitates are largely composed of arsphenamin or neo-arsphenamin rather than of serum proteins, and are readily dissolved by the addition of traces of sodium hydroxid.

A STUDY OF THE SPINAL FLUID IN ONE THOUSAND EIGHT HUNDRED AND SIXTY-NINE CASES OF SYPHILIS IN ALL STAGES

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In 1913, with the installation of the syphilis clinic at the University of Michigan, a study of the spinal fluid in all cases of syphilis was begun. Previous to this time important contributions suggesting the frequency of involvement of the nervous system in early syphilis had already appeared in the literature in France by Ravaut,[1] in Germany by Altman and Dreyfus,[2] and in this country by Engman[3] and his co-workers. In 1914 and 1915 studies from this clinic appeared on the involvement of the nervous system, particularly in reference to the secondary period of the disease, by Wile and Stokes.[4] The results of these studies showed that the invasion of the nervous system occurred extremely early, that it was frequently seriously involved without symptoms, and that serious involvement might escape detection unless the routine lumbar puncture was practiced on all cases. The high percentage of involvement in early syphilis led us at that time to state our belief that "the fate of every syphilitic with regard to the incidence of cerebrospinal lues, whether this occurs early or late in the course of the disease, is determined in the first months of the infection." Our results in the main have been confirmed by the contemporary writers and subsequent publications.

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1. Ravaut: Ann. de dermat. et syph., Ser. 4, No. 2:1 and 537; 1903; Ser. 4. No. 5:1057, 1904; Ser. 4, No. 8:1057, 1907; Rev. mens. d. méd. inst., No. 3:1. 1909.

2. Altman and Dreyfus: München. med. Wchnschr. **5**:465, 1913. Dreyfus: München. med. Wchnschr. **59**:2567, 1912.

3. Engman, M. F.; Buhman, R.; Gorham, F. D., and Davis, R. H.: A Study of the Spinal Fluid in One Hundred Cases of Syphilis, J. A. M. A. **61**:735 (Sept. 6) 1913.

4. Wile and Stokes: A Study of the Spinal Fluid with Reference to Involvement of the Nervous System in Secondary Syphilis, Dermat. Wchnschr. **59**:1079, 1107 and 1128, 1914.

At present we have at our disposal, for the purpose of study, 1,869 cases of syphilis in all stages, on which routine lumbar punctures have been carried out, together with careful study of the associated findings. This number represents about one third of the total number of cases of syphilis seen during this period.

The cases included in this group have been selected particularly with reference to correct diagnosis, and the number is limited to those that have been accurately observed over a definite period of time. Cases of doubtful diagnosis and cases seen casually have been cast aside.

TYPES OF SYPHILIS STUDIED

According to the clinical findings, the cases have been divided into the following types: congenital syphilis, primary syphilis (chancre only present), secondary syphilis, late syphilis of the skin and mucous membranes (tertiary), latent syphilis, tabes, general paresis, taboparesis and diffuse cerebrospinal syphilis. In Table 1 will be found the number of cases in each group.

TABLE 1.—CLASSIFIED TYPES OF CASES

Type of Syphilitic Involvement	Number of Cases
Congenital	53
Primary	236
Secondary	508
Tertiary	155
Latent	568
Diffuse cerebrospinal	178
Tabes dorsalis	109
General paresis	49
Taboparesis	13

TABLE 2.—NUMBER OF CASES WITH PLEOCYTOSIS AS FOUND IN VARIOUS TYPES OF SYPHILIS STUDIED, WITH THE PERCENTAGE INVOLVEMENT

Type of Syphilitic Involvement	Number of Cases	Number With Increased Cells	Percentage With Increased Cells
Congenital	53	14	26.4
Primary	236	38	16.1
Secondary	508	173	34.0
Tertiary	155	39	25.1
Latent	568	163	28.6
Diffuse cerebrospinal	178	157	88.2
Tabes dorsalis	109	102	93.5
General paresis	49	47	95.9
Taboparesis	13	13	100.0

The ordinary criteria, as now accepted, indicating the involvement of the nervous system are the standards used in this study. Thus, a cell count of over 6, the presence of increased albumin and globulin and the Wassermann test on the spinal fluid are considered, as well as the Lange gold curve in a certain number of selected cases.

In order to determine the parallelism, if any exists, between the various criteria, separate tables are given. Table 2 shows the percentage of involvement as indicated by increased cell count. Table 3 indicates the percentage of involvement as shown by increased globulin and albumin content in the fluid. Table 4 shows the percentage of involvement as indicated by the positive Wassermann test on the fluid.

TABLE 3.—NUMBER OF CASES WITH INCREASED ORGANIC SOLIDS AND THE PERCENTAGE OF INCREASE IN THE VARIOUS TYPES STUDIED

Type of Syphilitic Involvement	Number of Cases	Number With Increased Albumin and Globulin	Percentage With Increased Albumin and Globulin
Congenital	53	7	13.2
Primary	236	45	19.0
Secondary	508	178	35.1
Tertiary	155	41	26.4
Latent	568	154	27.1
Diffuse cerebrospinal	178	173	97.2
Tabes dorsalis	109	107	98.1
General paresis	49	47	95.9
Taboparesis	13	13	100.0

TABLE 4.—NUMBER OF CASES WITH A POSITIVE WASSERMANN REACTION OF THE SPINAL FLUID AND THE PERCENTAGE WITH POSITIVE REACTIONS IN THE VARIOUS TYPES STUDIED

Type of Syphilitic Involvement	Number of Cases	Number With Positive Wassermann Reaction	Percentage With Positive Wassermann Reaction
Congenital	53	9	16.9
Primary	236	14	5.9
Secondary	508	135	26.5
Tertiary	155	48	30.9
Latent	568	159	27.9
Diffuse cerebrospinal	178	156	87.6
Tabes dorsalis	109	102	93.5
General paresis	49	47	95.9
Taboparesis	13	13	100.0

From a study of these tables it will be seen that in each group of cases a fair degree of parallelism exists in the ratio of involvement, as shown by each of the criteria. In the main, the increase in globulin is found slightly more frequently than any other single finding, and this increase was almost constantly parallel with an increase in the number of cells present. A slightly lower percentage of involvement is seen in the column of Wassermann tests.

From the standpoint of delicacy of all tests, general paresis and taboparesis yield the highest percentage, 100 per cent being found positive in all columns in the combined type and 95 per cent. in all columns in the straight, frank paresis. Tabes is slightly lower and the diffuse form of cerebrospinal syphilis ranks last in the uniformity of positive criteria, although still showing a high percentage of parallelism with the clinical findings.

The material included in this study presents many interesting points of discussion, each one of which might well be the subject of a separate paper. It is expected that these will so be treated in the near future. In this particular study we wish to emphasize three distinct interesting points that have been brought out in our analysis of the cases. First: The strikingly high percentage of neurosyphilis associated with syphilitic alopecia, iritis and leukoderma colli. Second: The association of neurosyphilis with late syphilids of the skin, bones and viscera. Third: The high percentage of asymptomatic neurosyphilis occurring during the indefinite period of latency.

NEUROSYPHILIS ASSOCIATED WITH SYPHILITIC ALOPECIA, IRITIS AND LEUKODERMA

Early in our study we were struck by the great frequency with which neurosyphilis, particularly as indicated by practically all criteria in the spinal fluid, was associated with syphilitic alopecia. From our cases of this complication we find that of forty-six cases showing this symptom, 73 per cent. had coincident involvement of the nervous system. Practically all cases in which involvement occurred were characterized by a considerable degree of pleocytosis. A few patients had symptoms of headache; none had distinct organic signs, except such indefinite ones as increased reflexes. Many with a high degree of involvement were absolutely without symptoms.

Alopecia as a complication occurred in about 6 per cent. of all of our secondary cases. The mechanism of specific alopecia is not clearly understood, and we suggest that this mechanism may actually relate, at least in some cases, back to a disorder of enervation, being associated with the coincident cerebrospinal envolvement, rather than due to a direct involvement of the hair follicle by spirochetes.

A similarly interesting and uniformly high association was found in the complication of secondary iritis. In our series this occurred in twenty-one of 508 secondary cases of syphilis studied. Associated cerebrospinal involvement occurred in fifteen of these twenty-one cases, or 71.4 per cent.

Of the more tardy secondary syphilids, a high percentage of involvement of the nervous system was found in association with leukoderma colli. Our figures of this manifestation are rather small, only eleven cases having been seen. Of this number, however, 55 per cent. were found distinctly positive in the spinal fluid.

NEUROSYPHILIS AND SYPHILIS OF THE SKIN, BONES AND VISCERA

We may turn now to the association of the central nervous involvement with other forms of late syphilis, particularly those of the skin, bones and viscera. It is a common teaching and a general belief that

an inverse ratio exists between cerebrospinal involvement and other forms of late syphilis. For example, it is believed that tabetics and paretic patients and patients with other cases of late neurosyphilis with outstanding symptoms are seldom seen with late manifestations in the splanchnic system or in the skin and bones. This belief is at least held by some to be clinical evidence suggesting the existence of spirochete neurotropism. Whatever the merits of the question of spirochete strains are, and certainly considerable evidence exists tending to substantiate their existence, we are convinced from our study that this question cannot find a reliable argument in the lack of coincidence of late neurosyphilis and other forms of gummatous involvement. Thus, we find that in 155 cases of late syphilis involving the skin and mucous membranes, the bones and the viscera in the form of gummas and diffuse syphilomas, forty-eight cases, or 30 per cent., showed involvement of the nervous system at the same time. We found a frequent association, for example, of tabes and hepatic syphilis and aortitis, and in a few cases, of paresis and tabes with definite gummatous lesions in the skin.

The predominance of the neurologic symptoms and signs in cases of late syphilis of the nervous system and the fact that many of these cases are studied merely from the angle either of their psychiatric or neurologic aspects has undoubtedly led to the failure to recognize coexistent visceropathies.

Our studies have for the most part been made when patients showed definite involvement of the viscera, the skin or bones and when on examination we have been able to demonstrate the coincident cerebrospinal disease. From an experience extending over eight years, during which time we have had occasion to examine cases of late cerebrospinal syphilis in all forms referred to us from other services, we have been similarly struck with fully as high a percentage of associated splanchnic, cutaneous and osseous syphilis when the cases are viewed from this angle.

NEUROSYPHILIS OCCURRING DURING PERIOD OF LATENCY

Studying our figures from the standpoint of the occurrence of cerebrospinal involvement with asymptomatic syphilis, we find that in the latent period of the disease about 28 per cent. of all patients showed distinct involvement, as shown by increased cell count, increased organic solids and the Wassermann reaction in the fluid. This group of cases is made up largely of patients who have consulted the hospital for reexamination as to a preexisting syphilis. A large part of this group, however, is composed of those who had entered the hospital for some other complaint and who had been referred to this department

on the basis of the positive Wassermann blood test. In this group, entirely asymptomatic from the standpoint of the nervous system as well as from the general constitutional manifestations, we found, studying these patients from the standpoint of the colloidal gold curve, that a number gave typical paretic curves, others the curve of tabes.

To state with any degree of definiteness that these asymptomatic patients would inevitably develop active manifestations is perhaps too dogmatic in the light of our present knowledge. Such cases, however, in which the existence of cerebrospinal involvement is unknown to the patient and makes itself known only through the lumbar puncture, findings are extremely important when viewed from the standpoint of the patient, the community and, in general, the prognosis of the disease. We believe that if these patients had been examined early in the course of the disease the involvement would have been demonstrated at that time and if through intensive treatment it had been directed to the nervous system, the patient might have been saved the later complication. In that particular type of case in which an acute meningeal reaction occurs early, with or without symptoms, we have been impressed with the rapidity with which the fluid can be restored to normal through intensive constitutional and intraspinal medication.

That some patients of this group, asymptomatic at the time of puncture, actually did develop symptomatic neurosyphilis, we were able to demonstrate in a few of the cases under observation for several years. Thus, for example, we have seen definite paretic symptoms develop in a few cases in which at the preliminary puncture the paresis was manifested only by the Lange gold curve.

CONCLUSIONS

1. The nervous system, if uninvolved as shown by the accepted criteria during the first months of the infection, is seldom invaded later. A negative preliminary puncture followed by positive findings at a later date occurred in only three of several thousand cases punctured.

2. Of the several criteria indicating involvement, the increase of organic solids is found to be slightly higher than either the cell count or the Wassermann reaction, the relative value being indicated in the order just mentioned.

3. A considerable degree of cerebrospinal involvement may be present in the latent period of syphilis without manifesting any signs or symptoms.

4. Such asymptomatic cases may become symptomatic later, and a study of the colloidal gold curve in these cases is of some value in estimating the ultimate prognosis of the case.

5. Comparing the large number of cases of primary and secondary syphilis in which positive findings are found, with the relatively small percentage of late neurosyphilis as compared to total syphilitic incidence, we must conclude that a large number of early cases are in the nature of a meningeal roseola, which is transitory in its clinical aspects.

6. The interpretation of the lumbar puncture findings, particularly early in the incidence of the disease, constitutes a valuable guide in estimating the ultimate prognosis of the disease with regard to the integrity of the nervous system.[5]

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5. In addition to the references already given, the following may be of interest:

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AN ATTEMPT TO IMPROVE THE SENSITIVENESS OF THE COMPLEMENT-FIXATION TEST FOR SYPHILIS WITHOUT LOSS OF ACCURACY

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It is a well-known fact that varying amounts of the antilipoidal substances of syphilitic serum which are responsible for the fixation of complement in the Wassermann reaction are lost in the process of inactivation. This accounts in part for the higher percentage of positive reactions obtained by some of the raw serum methods, as compared with the classic Wassermann test. That there is a general desire for a more sensitive test is indicated by the numerous complement-fixation tests with noninactivated serum that have been employed. There is, however, a prevailing distrust of raw serum methods for routine diagnosis on account of the risk of false positive reactions—and not without reason. If a test can be devised that will be as free from the possibility of false positive reactions as is the Wassermann test and at the same time be as delicate as the better known raw serum tests, such as the Noguchi and Gradwohl, it will fill a real need. I shall describe a test that I believe has this degree of safety with the advantage of greater delicacy.

RELATIVE MERITS OF GUINEA-PIG AND HUMAN COMPLEMENT

In a reliable raw serum test the native complement present must be taken into account and used to best advantage. As having a bearing on one of the claims of superiority of such a test, the relative merits of guinea-pig and human complement is the first subject for consideration.

The most important advantage of human complement is its greater fixability by antigen-antibody combination as compared with that of guinea-pig serum. This property of human complement plus the larger quantity of antibody in noninactivated serum yields positive reactions that would escape a heated serum and guinea-pig complement method, and converts weak reactions into strong ones.

The second advantage of human complement is that, being a normal constituent of human serum, it is not subject to serious anticomplementary action on the part of the patient's serum. Means for eliminating this difficulty entirely are provided for in the test to be described.

Guinea-pigs can be dispensed with entirely if human serum is used.

As to the disadvantages: Human complement is said to be more susceptible to nonspecific fixation by antigen plus serum than is guinea-pig complement; it therefore follows that means must be provided in a satisfactory raw serum test to guard against the occurrence of falsely positive results from this cause. In tests utilizing only the complement of the serum to be tested, the precaution of titration with antigen cannot be carried out as it is impossible even with a testing of each serum to titrate the complement in a positive serum in the presence of antigen.

Lack of fixability, but with full lytic activity, occurs ocasionally with the complements of individual persons and also of guinea-pigs, resulting in false negative reactions. This is one of the drawbacks of a system employing the natural complement of the serum tested, and accounts for the occasional false negative results in raw serum systems that should theoretically reveal the smallest traces of syphilitic amboceptor. False negatives of this kind occur with tests like the newer Noguchi, Gradwohl, Thompson, and, in fact, with practically all of the raw serum methods and with all others using complement from a single animal.

The next consideration is the hemolytic system. Human and sheep cells are used almost exclusively and, for various reasons, principally of convenience, doubtless will continue to be used to the practical exclusion of others. According to Kolmer, Matsunami and Rule,[1] the antihuman hemolytic system is somewhat more sensitive than the anti-sheep, but this is more pronounced in high dilutions of positive serums than in the usual quantities. This slight advantage, and also whatever advantage may reside in the greater availability of human blood, is more than counterbalanced by the difficulty of obtaining a high titer antihuman rabbit serum and the annoyance of the presence of agglutinins for human cells both in the rabbit serum and in the test serum. These agglutinins are probably partly responsible for the false positive reactions obtainable occasionally with the Noguchi test. Where it is necessary to fortify the complement content of the serum by the addition of fresh negative serum, the difficulty is increased proportionately.

ADJUSTMENT OF REAGENTS

Means for the reasonably accurate adjustment of the factors of the hemolytic system are essential to a reliable test. It is true that such tests as the Hecht-Gradwohl, in which both native complement and

1. Kolmer, J. A.; Matsunami, T., and Rule, A.: Standardization of the Wassermann Reaction, A Comparative Study of Complement Fixation in Syphilis with Antihuman, Antichicken and Antisheep Hemolytic Systems, Am. J. Syph. 4:278 (April) 1920.

native amboceptor are utilized, are quite accurate, for although the ratio between complement and amboceptor are unknown, the practical equivalent is obtained in the finding of the hemolytic unit. Theoretically, if the test serum should be strong in hemolysin, the lytic unit would contain such a small amount of complement as to be absorbed nonspecifically, thus giving false positive reactions.

The adjustment of the hemolytic system is of great importance, not only in regard to the balance between complement and amboceptor, but also between the size of the unit of these reagents in relation to the volume of test serum employed. If the complement is titrated against a fixed amount of amboceptor and this amount is unduly large, the unit of complement may be so small as to be absorbed nonspecifically. On the other hand, if the unit of complement is too large, a positive serum may be unable to fix the whole amount, thus causing a weaker reaction than would have been obtained with the proper adjustment. If the amount of patients' serum is too small in proportion to the other ingredients, delicacy of reaction is lost by inability of a weak serum to absorb all the complement. If the amount of patients' serum is too large in proportion to the elements of the hemolytic system, false positives may result from loss of complement through partial nonspecific fixation by the serum-antigen mixture. An excess of amboceptor may be present in those methods in which an antisheep system is used without taking into account the native amboceptor in the patients' serum. The methods of Stern and of Hecht and the original Wassermann test are subject to this criticism. Excess of amboceptor is capable of dissociating complement and thus rendering tests less delicate. Seelman [2] has devised a raw serum method in which the amount of complement and native amboceptor are both estimated in an ingenious manner, but it is too complicated for the rank and file of serologists. It should, however, be fairly safe against false positives since the adjustment of the hemolytic system is such that foreign complement has frequently to be added.

While it is desirable that a system should have as few false negative reactions as possible, it is more important that it should not be subject to the danger of false positive reactions. The present system, while capable of giving a very small percentage of false negative reactions as is true of other human complement methods, has an advantage over those in which noninactivated serum with complement from a single individual is used—such as the Noguchi and others depending on the use of very fresh serum—the adjustment of the hemolytic system being such as to avoid the necessity of adding any foreign complement. This point will be more fully brought out in the description of the technic.

2. Seelman, J. J.: A Raw Serum Wassermann Test Employing the Sheep Hemolytic System, Am. J. Syph. **4**:157 (Jan.) 1920.

TECHNIC OF THE PROPOSED METHOD

Hemolytic System.—Sheep's blood is washed three times and the measure made up to the original volume of the blood. For use in the test and in titrating reagents it is diluted five times, making a 20 per cent suspension.

Amboceptor.—This is made up of rabbit antisheep immune serum standardized by titration of varying dilutions in amounts of 0.2 c.c. against 0.2 c.c. of 20 per cent. guinea-pig serum, pooled from several pigs, and from two to four hours old on the clot, and 0.2 c.c. of 20 per cent. suspension of sheeps' blood with salt solution to make 2.0 c.c.

Complement.—This is composed of human serum, pooled from the negative serums of the previous days' tests and titrated against the unit of amboceptor before each test, or guinea-pig serum pooled from several pigs and titrated in the same manner. If human serum is used, it must be de-amboceptorized, as described later. In either case, the unit of complement is 0.2 c.c. of the weakest dilution just giving complete hemolysis of 0.2 c.c. of 20 per cent. blood with one unit of amboceptor in 10 minutes.

Antigen.—The antigen used is Noguchi's acetone insoluble. It is advisable to standardize the antigen with human complement if the latter is to be used, and to prepare dilutions for the test containing five antigenic units in 0.2 c.c., the amount used in the test.

Patients' Serum.—Five-tenths c.c. of the serum to be tested is placed in a tube and 0.5 c.c. of a 33 per cent. suspension of whole sheep's blood is added. The tubes are immediately placed in cracked ice. Melting ice has a temperature of 1 C., at which point the amboceptor is fixed, but not complement, and no hemolysis takes place. After standing one hour in the ice, the tubes are centrifuged and the clear serum pipetted off into the tubes for the test.

The process of removing the natural amboceptor from the serum in a laboratory properly equipped with a high speed centrifuge is no trouble whatever. The tubes are placed, three or four in each of the eight holders. (Most machines are equipped with an eight place head.) A few seconds after the motor has reached full speed, the current is shut off and it will be found that the cells are packed in the bottom of the tubes, which are returned to the ice water until pipetted off into the tubes for the test. Most of the time required for this process is consumed in pipetting off the serums from the clots, and adding the sheep cells. The time required in weighing up the tubes, placing in the machine, whirling and then removing is not more than twenty minutes for fifty specimens.

Preliminary Titration.—As before stated, the value of the antisheep amboceptor is established in the beginning, and thereafter a fixed quan-

tity is used for titrating complement and in the test. If guinea-pig complement is to be used, dilutions of 1 to 5, 1 to 6, 1 to 8, and 1 to 10 are made up as follows:

TABLE 1.—GUINEA-PIG COMPLEMENT

Guinea-Pig Serum, C.c.	Salt Solution, C.c.	Dilution
0.1	0.4	1 to 5
0.1	0.5	1 to 6
0.1	0.7	1 to 8
0.1	0.9	1 to 10
0.1	1.1	1 to 12

A row of five tubes is set up and in each is placed one of the complement dilutions, 0.2 c.c., amboceptor dilution of the titer strength, 0.2 c.c. (1 unit), sheep's blood (20 per cent), 0.2 c.c., and salt solution 1.4 c.c.

If human serum is used for complement, it is first de-amboceptorized by adding one part of whole blood to three parts of serum, chilling and centrifuging as already described. In its titration, four tubes are set up containing, respectively, 0.2, 0.15, 0.1 and 0.05 c.c. of the serum; otherwise the process is the same as for guinea-pig serum. The smallest amount causing complete hemolysis in ten minutes has the value of one unit.

Setting Up the Test.—Three tubes only are required for the test. In addition to the test serums, a positive control should be set up. The back tube is for the purpose of estimating the amount of complement present in the serum and for the anticomplementary control. The two front tubes are for the test proper. Into each of the three tubes is placed 0.2 c.c. of the de-amboceptorized patient's serum, which contains 0.1 c.c. of undiluted serum. The front and middle tubes receive in addition 0.2 c.c. of antigen and 1.0 c.c. of salt solution, and the front tube receives one-half unit of complement. The back tube receives, besides the serum, 0.2 c.c. of amboceptor dilution of such strength that it contains one and one half units, 0.2 c.c. of sheep cells, (20 per cent. blood) and 1.4 c.c. of salt solution. The tubes are placed in the 37 degrees bath for preliminary fixation of whatever complement may be present in the first two tubes, and to estimate the amount of complement present by the rate of hemolysis in the back tube. This can be gaged closely as the exact amount of amboceptor is known. On the rate of hemolysis depends the decision of how much complement to add to the front and middle tubes. The plan is to have one half unit of complement in the front tube in excess of the amount in the middle tube. The object of this is, first, to facilitate the reading of

results: Since the strength of reaction is a measure of the fixing power of antibody-antigen, it follows that strongly positive serums will bind all the complement in both tubes, whereas a weaker one may fix the complement in the middle tube but not all in the front tube. The reading of results is, therefore, much easier as well as more accurate than when one tube only is used, but the most important function of the excess of complement in the front tube is to introduce a pooled complement into the test, thereby guarding against the chance of false positive reactions.

TABLE 2.—Complement Fixation Test

Front Tube	Middle Tube	Back Tube
First incubation, 10 minutes		
Serum ..... 0.2 c.c.	Serum ..... 0.2 c.c.	Serum ..... 0.2 c.c.
Complement, ½ unit		Amboceptor ..... 0.2 c.c.
Antigen ..... 0.2 c.c.	Antigen ..... 0.2 c.c.	Sheep cells..... 0.2 c.c.
Salt solution.....1.0 c.c.	Salt solution.....1.0 c.c.	Salt solution.... 1.4 c.c.
Continuation of first incubation, 20 minutes		
Comp. q. s.	Comp. q. s.	Comp. q. s.
Second incubation, 15 minutes		
Amboceptor ..... 0.2 c.c.	Amboceptor ..... 0.2 c.c.	Amboceptor ..... 0.2 c.c.
Sheep cells..... 0.2 c.c.	Sheep cells..... 0.2 c.c.	Sheep cells..... 0.2 c.c.

Individual complements sometimes possess the peculiar property of nonspecific absorption by antigen plus serum, the control tube without antigen clearing up. In this event the extra foreign complement in the front tube causes complete hemolysis, and no mistake occurs. Having placed the tube racks in the water bath, the rear tubes should be inspected at frequent intervals. If hemolysis occurs in four minutes, in the presence of 1½ units of amboceptor, it indicates the presence of one unit of complement; hemolysis in from six to seven minutes means one half unit and in from twelve to fourteen minutes, one fourth unit. At the end of ten minutes, one fourth unit of complement is added to all three tubes of those sets in which hemolysis is not quite complete in the back tube and one half unit to those sets in which hemolysis is slight. Any tubes not completely hemolyzed in another ten minutes are anticomplementary and another half unit should be added. In the case of persistently anticomplementary serums, this should be repeated at intervals of ten minutes until hemolysis is complete. Anticomplementary results are thus elminated entirely. Incubation is continued for twenty minutes after the last addition of complement and blood, 0.2 c.c., and amboceptor, 1½ units, are added to the first two tubes. The results are read fifteen minutes after the addition of cells and amboceptor.

Reading of Results.—Complete inhibition in the second tube is a definite or +++ positive reaction, provided inhibition is marked in the first tube.

Complete hemolysis in the first tube should cause one to regard with suspicion any inhibition in the second tube as possibly being due to nonspecific fixation. If, under these circumstances (complete hemolysis in the first tube), the hemolysis is only partial in the second tube, the result may be accepted and recorded as + or ++, as the case may be. If, however, there is no hemolysis in the second tube and complete hemolysis in the first tube, the safest plan is to reject the result entirely.

Almost complete inhibition in the second tube, with a varying degree, but less, in the first tube, is a ++ reaction.

A + reaction, as before stated, is recorded when the inhibition in the second tube is slight but definite.

The control tubes must, of course, be clear in all cases.

ADVANTAGES CLAIMED FOR THE METHOD

1. It is a raw serum method, consequently more delicate than is possible for an inactivated serum method.

2. The amounts of both complement and amboceptor are known and controlled.

3. False negatives from an insufficient amount of complement are impossible.

4. The method is applicable to all serums, regardless of age or the amount of complement contained, and to spinal fluids.

5. It is as simple and no more time consuming than the regular Wassermann test.

6. False positive reactions, which are due to nonspecific fixation either from too small an amount of complement or on account of peculiar properties of individual complements, are impossible because of the use of two antigen tubes, one of which contains pooled complements in excess of hemolytic requirements. The use of acetone insoluble antigen removes the last vestige of chance for false positive reactions.

7. No anticomplementary results are obtained.

THE SACHS-GEORGI REACTION FOR SYPHILIS

A PRELIMINARY REPORT OF MORE THAN ONE THOUSAND COMPARATIVE WASSERMANN AND SACHS-GEORGI TESTS *

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The Wassermann reaction for syphilis, despite its wide clinical acceptance, cannot be regarded as free from certain inherent defects. The mere fact that the test requires a considerable number of biologic reagents for its performance, all of which are to some degree variable and uncertain, is perhaps one of the reasons that the results of the test are not always reliable even when in the hands of the conscientious worker. We must furthermore recognize that a definite number of cases clinically positive are serologically negative. The standardization of the biologic reagents might seem a logical improvement, and efforts are being made in this direction by the German authorities. Efforts to simplify the technic have repeatedly been made, particularly since the recognition that the reaction is essentially physicochemical, not depending on specific immunologic alterations in the serum of the syphilitic. Perhaps the flocculation reactions, such as those described by Porges and Meyer, Herman-Perutz, Bruck, Klausner and others, gave evidence of progress in this direction, although none of them offered a real substitute for the Wassermann test.

The increased use of tests for syphilis, as well as the general shortage of the necessary biologic reagents incident to the war, made a reinvestigation of the problem desirable. Two tests have been developed: that of Meinicke,[1] and that of Sachs-Georgi,[2] which are evidently of considerable usefulness. Of these, the Sachs-Georgi, because of its remarkable simplicity as well as its seeming specificity, has found most favor. The obvious importance of simplified serologic procedure would warrant a careful comparison of such tests with the Wassermann reaction, and we have therefore examined over one thousand serums and spinal fluids by the Sachs-Georgi technic.

TECHNIC

The technic of the Sachs-Georgi test which we have employed is the modification proposed by Mandelbaum,[3] which differs from the

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1. Meinicke, E.: Berl. klin. Wchnschr., **55**:83, 1918.
2. Sachs, H., and Georgi, W.: Med. Klin. **14**:610, 1918.
3. Mandelbaum, M.: München. med. Wchnschr. **65**:294, 1918.

original in the use of smaller amounts of serum and antigen. The serum or spinal fluid to be tested must be absolutely clear after being centrifuged, free from cotton fibers or other particles. It is inactivated in the water bath at 56 C. for one half hour. Three drops of serum are then mixed with 1 c.c. of sterile salt solution (0.85 per cent.). To this diluted serum, 0.5 c.c. of cholesterinized alcoholic beef heart antigen, which has been previously diluted 1 to 6 with 0.85 per cent. salt solution, is added. The tubes are then gently agitated and placed in the incubator at 37 C. for from eighteen to twenty-four hours. A reading is taken at this time; most of the positive serums will have flocculated. The tubes are kept at room temperature for the next twenty-four hours, and final readings are then made.

Apparatus.—Glassware must be perfectly clean. We have our tubes washed in tap water, then placed in an acid cleaning bath for several hours, washed in tap water and finally rinsed several times in distilled water. They are then dried in the hot air oven. Sterile pipets are used.

Serum.—The question that has been raised in the Wassermann technic concerning the use of active or inactive serum is also involved in the Sachs-Georgi test. Mandelbaum dilutes the fresh serum and then inactivates it before adding the antigen. We have used the inactivated serum, then diluted and added the antigen. Other observers prefer to keep the serum on ice several hours before inactivating assuming that because of certain alterations brought about by the chilling of the seroglobulins, the reaction is made more sensitive.

Diluting Agents.—In the Wassermann reaction, approximate isotonicity seems sufficient, minor variations in the concentration of the salt being without effect on the reaction. In the Sachs-Georgi reaction we have found that reliable results can be obtained only when the salt solution is made up to 0.85 per cent. The salt solution should, of course, be sterilized.

Antigens.—The preparation of the proper antigen is perhaps the fundamental factor in the success or failure of the Sachs-Georgi reaction. Extracts from human, beef, pig, guinea-pig and sheep heart have been used, as well as from beef and syphilitic fetal liver. Our most satisfactory results have been obtained with an antigen thus prepared: Beef heart cut into small pieces was ground in a meat grinder; 5 c.c. of alcohol (95 per cent.) per gram of moist heart substance was then poured over the mass and incubated at 37 C. for from eight to ten days. During this time the flask was shaken each day. The alcoholic extract was then filtered and cholesterinized. The amount of cholesterin needed varies with each antigen. We have found it good practice to titrate the antigen against positive and neg-

ative serums after adding various dilutions of cholesterin to small fractions of the antigen and selecting the proper amount of cholesterin to be added according to our actual serum titration. Sachs and Georgi thus prepared their antigen: To 100 c.c. of filtered beef heart extract and 200 c.c. of alcohol is added 13.5 c.c. of a 1 per cent. alcoholic solution of cholesterin.

Before use the antigen is diluted 1:6 with salt solution. The dilution must be made neither too slowly nor too rapidly. The extract when properly made is quite clear, the diluted antigen faintly opalescent and does not flocculate after standing several days. The antigen when diluted 1:10 serves very well as an antigen for the Wassermann reaction.

Incubation.—In the original Sachs-Georgi technic, the tubes were incubated for two hours and then placed at room temperature for twenty-four hours. Mandelbaum, Hauck,[4] Ammenshauser [5] and others have shown that better results are obtained if the incubation is prolonged for from eighteen to twenty-four hours. The tubes are then read and kept at room temperature for another twenty-four hours before the final reading is made. Sachs and Georgi have adopted this modification.

Reading of Results.—Most of the German workers have used the agglutinoscope devised by Kuhn and Voit to read the results. A good magnifying lens from a dissecting microscope or even the ocular from a microscope can, however, be used with very satisfactory results if the tubes are held against a dark background. The flocculation may be very fine—smoky, finely granular—driven snow, or may finally be precipitated at the bottom of the tube as a coarsely granular floccular mass. Gentle rotation or agitation of the tube aids observation. Negative cases remain perfectly clear for twenty-four hours, later a slight precipitate may collect at the bottom of the tube, but this can readily be differentiated from positive findings. In a general way, one can grade the degree of the reaction on a one to four plus basis; in a few cases we have recorded plus-minus readings. With the use of the agglutinoscope, the number of doubtful readings would probably be increased. We have found it useful to centrifuge doubtful tubes at low speed for half an hour and then pour off some of the supernatant fluid. By comparison with negative tubes similarly treated, minor differences become more apparent. We have also kept the tubes on ice after incubation, but have found no superiority over simple room temperature from this procedure.

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4. Hauck, L.: Influence of Temperature on Sachs-Georgi Reaction, München. med. Wchnschr. **67**:369 (March 26) 1920.

5. Ammenshauser: Centralbl. f. Bakteriol., **84**:521, 1920.

RESULTS OF EXAMINATION

In Table 1 are recorded the results of 1,042 examinations made with the Wassermann and the Sachs-Georgi tests. The serums and cerebrospinal fluids were obtained from the serologists of the Cook County Hospital and the city board of health; their Wassermann reports were based on tests with from two to four antigens.

TABLE 1.—RESULTS WITH WASSERMANN AND SACHS-GEORGI TESTS

Reaction	Result								
Wassermann	Positive			Negative			Anticomplementary		
Sachs-Georgi	+	±	−	+	±	−	+	±	−
	163	5	3	44	9	634	2	0	3
Total					866				

In Table 1 it will be observed that in 163 cases there was an agreement of positive cases (18.8 per cent.) and in 634 an agreement of negative cases (73.2 per cent.), i. e., an agreement of 92 per cent.

The results with cerebrospinal fluids are given in Table 2

TABLE 2.—RESULTS WITH CEREBROSPINAL FLUID

Reaction	Result								
Wassermann	Positive			Negative			Anticomplementary		
Sachs-Georgi	+	±	−	+	±	−	+	±	−
	36	6	3	7	2	121	1	0	0
Total					176				

The total agreement in this series was 157, or 89.2 per cent.

Of the total number of serums and cerebrospinal fluids examined (1,042), sixty-two were found to give a positive or plus-minus Sachs-Georgi reaction while the Wassermann was negative. The details in our possession concerning these cases are recorded in Table 3.

It will be observed that the clinical history or the physical findings in thirty-six of these patients made a diagnosis of syphilis probable (58 per cent.). In twenty, the reaction seems nonspecific (32 per cent.), while in six cases we have no information that would assist in the determination of the correctness of the serologic finding.

From a summary of 17,186 serum tests reported by a number of observers and collected by Baumgartel [6] (to which are added the 7,000 reported by him), Table 4 has been constructed.

It will be observed that in 5,808 positive cases and in 15,950 negative cases, there was complete agreement, as well as in 246 doubtful reactions, 91 per cent. of the total. Of the discrepancies (9 per cent.),

6. Baumgärtel, T.: Parallel Wassermann and Sachs-Georgi Tests, München. med. Wchnschr. **67**:421 (April 9) 1920.

TABLE 3.—Clinical Correlation of Cases with Positive Sachs-Georgi Reaction and Negative Wassermann Reaction

No. of Patient	Clinical Diagnosis on Admission	Clinical History	Treatment
xi-16	Suspected syphilis	Gonorrhea twice; chancre two months ago; now in second stage	None
ix-3	Chancroid	Primary syphilis; inguinal and epitrochlear glands enlarged, ulcer of scrotum	None
ix-32-34	Cerebral hemorrhage	History of chancre; rigid, irregular pupils; spinal fluid examination: pressure +++, globulins ++, 88 lymphocytes	None
ix-33	Cerebral hemorrhage	Paresis, left leg; patellar reflexes, +++; absent abdominal and cremasteric reflexes	Potassium iodid and mercury
viii-12	Acute arthritis	History of transient attacks of paraplegia; roentgen-ray, hypertrophic osteoarthritis; denies syphilitic infection	Improved under potassium iodid
viii-26	Chronic nephritis and endocarditis	Gonorrhea once, denies syphilis; pupils sluggish to light; absent patellar and cremasteric reflexes; shuffling gait; wife one miscarriage	None
vii-37	Bronchopneumonia and syphilis	Gonorrhea and buboes; punched-out scar on prepuce; slight adenopathy; epitrochlear glands	Intravenous medication 11/9/20 N. W. U. Post-Grad. M. Sch.
vii-64	General paresis	History of chancre and secondary syphilis; gastric crisis; tabetic gait and urinary incontinence; loss of memory	None
vi-8	General paresis	Chancre fourteen years ago; syphilitic erosion of nose; incontinence of urine; difficulty in walking at night; gastric crisis; patellar reflex, ++; Romberg sign, ++; Argyll Robertson pupils and scanning speech	Now on syphilitic treatment
vi-11-52	Syphilitic thrombosis	Chancre fifteen years ago; hemiplegia; amnesia; pupils sluggish; eyelids drooping; spinal fluid examination: pressure ++, globulin +, 16 cells	Has had six injections of arsphenamin
vi-24	Syphilitic epiphysitis	Congenital syphilis; palmar and plantar desquamation; rhagades about mouth; suggestive syphilitic nose	None
vi-51	Crossed paralysis of sixth and seventh cranial nerves	Chancre two years ago; paralysis, right side of face; secondaries, hands and face; spastic and ataxic gait; Romberg, +++; patellar, +++; spinal fluid examination: pressure ++, globulins ++; 12 cells	None
v-11	Syphilitic genital ulceration	Pregnant twenty times in twenty years; sixteen miscarriages, usually at two or three months	None
v-13	Chronic alcoholism, suspected tuberculosis	Chancre thirty-two years ago; rash twenty years ago; scars on penis, back and head	None
iii-1	Myocarditis; cardiac asthma	Chancre ten years ago; aneurism arch aorta	Arsphenamin 6 times, potassium iodid and mercury
iii-8	Syphilitic organic heart disease; general paresis	Perforated nasal septum; aortic regurgitation; tertiary syphilis; paresis, left side of face; cataract and posterior synechiae; aneurysmal dilatation of aorta	Syphilitic treatment, potassium iodid and mercury
iii-9	Cancer of stomach	Chancre four years ago; patellar reflex weak; gastric crisis	None
xii-58	Malaria	Chancre one year ago.....	None
xii-32	Hydrocele (syphilitic)	Chancre four years ago; secondary syphilis three years ago	None
xiii 23-50	Cerebrospinal syphilis	Chancre twenty-five years ago; loss of memory; scar on penis; drooping eyelids	None
xii-49	Chancre	Chancre three weeks ago.....	None
xiii-15	Acute epididymitis	Chancre three years ago; chronic gonorrheal urethritis; prostatic seminal vesiculitis and epididymitis	None
xiv-75	Cerebral syphilis	Chancre twenty-five years ago; Argyll Robertson pupils; spinal fluid examination: globulins ++, 80 cells	None
xiv-9	Traumatic epilepsy	Chancre twenty-four years ago; scar on penis and body	None

TABLE 3.—(*Continued*)

CASES IN WHICH THERE WAS NO COMPLETE RECORD AVAILABLE FROM HOSPITAL SOURCES, MOST OF THE SERUMS BEING OBTAINED FROM THE OUTPATIENT DEPARTMENT

	Clinical Diagnosis on Admission	Clinical History	Treatment
xii-49	.....	History of chancre.....	None
xiii-15	Syphilis	History of chancre.....	None
i-55	Tertiary syphilis	.....	None
ix-15	Fract. mandible	History of chancre.....	None
xii-4P	Syphilis	History of chancre.....	One injection
i-46	Tabes	.....	None
v-11	Syphilitic ulcer of leg	.....	None
xiv-2	Pulmonary tuberculosis and syphilis	History of chancre.....	None
i-6	.....	Chancre on lip.....	None
i-9	.....	History of chancre fifteen years ago.....	None
i-13	Syphilis	.....	None
xiii-62P	Syphilis	Syphilis.....	Treated case

TWENTY CASES IN WHICH THE WASSERMANN REACTION WAS NEGATIVE BUT THE SACHS-GEORGI POSITIVE WITHOUT ANY EVIDENCE OF SYPHILIS ON THE PART OF THE PATIENT, EITHER IN THE HISTORY OR CLINICAL FINDING

	Diagnosis or Symptoms		Diagnosis or Symptoms
iv-10	Pain in legs; optic neuritis	xiii-4	Bronchitis; asthma
vii-69	Dementia praecox	xiii-1	Typhoid
vii-66	Chronic alcoholism	xiv-30	Chronic nephritis
viii-22	Routine; no diagnosis	xiv-33	Bilateral salpingitis
viii-15	Ovarian cyst	xiv-54	Chronic bronchitis
ix-28	Routine; no diagnosis	xiv-55	Suspected carcinoma of colon
xii-31	Routine; no diagnosis	xiv-29	Routine; no diagnosis
xiii-24	Lobar pneumonia	xiv-13	Cerebral hemorrhage
xiii-14	Acute cystitis	xiv-8	Constipation
xiii-10	Acute gonorrhea; lobar pneumonia	xvii	Chronic arthritis and myocarditis

In six serums obtained from the serologist of the City Health Department, we obtained a positive Sachs-Georgi reaction with a negative Wassermann. These serums are sent in without diagnosis and we have no information concerning them.

TABLE 4.—RESULTS OF SERUM TESTS

Reaction	Result								
	Positive			Negative			Doubtful		
Wassermann.....	+	±	—	+	±	—	+	±	—
Sachs-Georgi.....	5,808	282	514	686	221	15,950	154	246	325
Total.....	24,186								

the cases in which the Wassermann reaction was positive and the Sachs-Georgi negative or doubtful, numbered 1,121, or 51 per cent.; those in which the Wassermann was negative while the Sachs-Georgi was positive or doubtful numbered 1,061, or 48 per cent. These collected results represent the observations made with various modifications of technic, particularly in regard to incubation time. The cases in which

the Wassermann reaction was negative while the Sachs-Georgi was positive include a considerable number of treated cases of primary and parasyphilitic disease, of congenital syphilis, as well as a small group of diseases of nonsyphilitic basis. The latter may possibly be eliminated with further study of the preparation of the antigen. Just as the Wassermann reaction becomes nonspecific to a considerable degree when the antigen is fortified with too much cholesterol, so perhaps the acuity of the Sachs-Georgi reaction can be modified when once we become familiar with its range.

DISCUSSION

An examination of the results tabulated herewith makes it evident that this flocculation test very closely approximates the results obtained with the classical Wassermann reaction and may in some ways prove superior to it. While for the time being we must accept the Wassermann test as our standard of comparison, we should by no means lose sight of the fact that this standard is not infallible. While the error does not lie in the direction of nonspecificity, a definite number of positive syphilitic cases do not react with the Wassermann technic and are either classed as negative or yield doubtful readings. It seems that this relatively large group of cases flocculate quite readily with the Sachs-Georgi method, as will be apparent from a perusal of some of the histories and clinical findings recorded in Table 2. Only in thirty-two cases of the series were the Sachs-Georgi reactions positive in the absence of positive clinical findings or history.

We can enter here but briefly into a discussion of the mechanism that seems to underlie the flocculation made grossly apparent in the Sachs-Georgi reaction, and which is closely related to the ultramicroscopic colloidal alterations that have been described as taking place in the Wassermann reaction when the antigen is added to the serum. Both the globulins and the lipoids of the syphilitic serum seem altered to some degree, and Schmidt,[7] Hirschfeld and Klinger,[8] Sachs,[9] and Meinicke[10] are of the opinion that the alteration involves a peculiar lipotropic property of the serum globulins, the lipoglobulin aggregate being easily precipitated in solutions that are iso-electric for the globu-

7. Schmidt: Ztschr. f. Hyg. u. Infectionskrankh. **69**:513, 1911.
8. Hirschfeld and Klinger: Ztschr. f. Immunitätsforsch. **21**:40, 1914.
9. Sachs, H.: Kolloid-Ztschr. **24**:123, 1919.
10. Meinicke, E.: München. med. Wchnschr. **66**:932, 1919.

lins. Neukirch[11] places the hydrogen-ion concentration represented in a 0.85 per cent. salt solution as the optimum for the precipitation of the globulins, i. e., the identical concentration found most satisfactory for use in the Sachs-Georgi technic. From the point of view of its theoretical interest, we wish to call attention to the two phase reaction of Meinicke[1] for syphilis. This reaction involves the precipitation of the globulins of the serum in both negative and positive serums by simple dilution after the addition of antigen; then the addition of varying dilutions of salt solution to the serums so altered. In positive cases, the lipoglobulin precipitate remains unchanged; in negative cases the precipitates redissolve.

The Sachs-Georgi reaction is exceptionally simple, and once a suitable antigen has been prepared, it can be carried out with ease. The use of the complement-amboceptor-hemolytic system used in the Wassermann reaction is after all a cumbersome method of making apparent the colloidal alterations which are at the basis of these reactions for syphilis. Ultimately such a system must be replaced by a reaction simpler in character, requiring fewer reagents and less manipulation. Whether such a reaction will be of the flocculation type, such as the Sachs-Georgi, or will be purely chemical, is for the present not in the range of discussion. It is evident, however, that the Sachs-Georgi, reaction, even in its present form, offers a valuable contribution because of its simplicity and its apparent practicability. The fact, too, that it is frequently positive in those syphilitic cases which do not give a positive Wassermann reaction makes it of value as an additional test to be used in conjunction with the Wassermann technic. The fact that a relatively small percentage of nonspecific reactions is obtained should not detract from its ultimate usefulness; the earlier work with the Wassermann reaction was handicapped until the preparation of antigens was better understood.

CONCLUSIONS

An examination of 1,042 serums and cerebrospinal fluids by means of the Wassermann and the Sachs-Georgi reactions demonstrated a close parallelism of the two reactions (92 per cent.).

In sixty-two cases in which the Wassermann reaction was negative while the Sachs-Georgi reaction was positive or doubtful, the clinical history or examination revealed evidence of syphilis in 58 per cent.

The technic of the Sachs-Georgi reaction is simple, only one biologic reagent is required (antigen) instead of the four used in the Wassermann test (antigen, amboceptor, complement and red blood

11. Neukirch, P.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **29**:498, 1920.

cells). This simplicity adds to the uniformity of the results. The ultimate specificity depends on the preparation of a proper antigen.

Because of its simplicity, and the fact that it is frequently positive in syphilitic cases when the Wassermann test is negative, we are of the opinion that the Sachs-Georgi reaction offers a valuable aid in the routine examination for syphilis when used in conjunction with the Wassermann reaction.

A SPURIOUS CHANCRE

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The case reported has a double interest, because it illustrates how perfectly an initial sclerosis may be mimicked by a factitial or benign inflammatory lesion, and how critical one may justly be of accounts of reinfections, superinfections and cures based on the excision of the chancre when the diagnosis of the lesion has been made on clinical criteria alone, without a complete confirmation by dark-field and serologic examination.

REPORT OF A CASE

History.—The case of C. P. (Case 295316) was diagnosed as tabes dorsalis, following an examination at the clinic in November, 1919. The spiral fluid Wassermann reaction was positive, the Nonne reaction was positive, and the lymphocytes numbered 140. The patient received six intravenous injections of arsphenamin, twenty intramuscular injections of mercury succinimid and interim treatment of forty mercurial inunctions. The patient, although repeatedly questioned, could give no history of a primary lesion, his first intimation that he had syphilis being in 1909, when his hair fell out in large amounts, and a quack told him that he had the disease. There was no sign of penile scar on first examination.

In June, 1920, this patient returned for further treatment. Supposing himself to be immune from the disease by virtue of having had syphilis, he had had a single intercourse with a clandestine prostitute six weeks before. Fourteen days later a papule appeared on the prepuce behind the corona, enlarging to half the size shown in the photograph and developing a superficial erosion before he gave it any attention. He then visited a physician who cauterized it twice with some mild chemical cauterant. The patient insisted that the only difference between the appearance of the lesion when cauterized and its appearance at the time of examination was in size.

Examination.—Examination disclosed the apparently typical initial sclerosis shown in the illustration. The base was smooth, the border faintly hemorrhagic, the exudate perhaps a trifle purulent, but serous after wiping with gauze. The induration was of the button type. There was no distinct inguinal adenopathy, although the discrete glands were palpable.

Three dark-field examinations were negative, two of them after saline soakings and one of them on aspiration of the base of the lesion. The Wassermann reaction of the blood was negative. The lesion was then excised and half of it sent to Professor A. S. Warthin of Ann Arbor, who reported that the pathology was that of a simple inflammatory reaction, not at all suggestive of syphilis, and that no *Spirochaeta pallida* could be identified in the tissue. In the meanwhile, an examination of the spinal fluid yielded positive Wassermann and Nonne reactions, 134 lymphocytes, and a colloidal gold curve of 0112222100.

The prostitute by whom the patient had been exposed was not accessible. Had she had active syphilis, with spirochete-containing lesions in the vagina, it is conceivable that the lesion in the patient might have been an inoculation gumma, since gumma-like lesions can be produced by the inoculation of living *Spirochaeta pallida* into the skins of patients with late syphilis.[1] The lesion could scarcely be interpreted clinically as a pseudochancre-redux in view of the previous

A spurious chancre with typical incubation, probably due to trauma and cauterization, in a patient with neurosyphilis.

treatment and in the absence of evidence of a former primary lesion at the same site or in its lymphatic drainage. The pathologic examination seems to eliminate both possibilities, as well as that of a superinfection. The lesion was evidently purely inflammatory, possibly in part at least an artefact due to cauterization. The perfection with which this spurious chancre mimicked the true Hunterian induration emphasizes the untrustworthiness of clinical, as distinguished from laboratory, criteria in the diagnosis of primary syphilis and in the determination of the status of reinfections and superinfections.

1. Landsteiner and Finger: Ueber Immunität bei Syphilis, Centralbl f. Bakteriol. **38**: Suppl. 107, 1906.

Correspondence

ARTIFICIAL LIGHT FOR PHOTOGRAPHY

To the Editor:—The difficulties of getting sufficient light for the taking of clinical photographs of dermatologic interest, which is feasible for office use, led me to try the air cooled mercury quartz lamp, which has become a fixture in almost all dermatologists' offices. My success has far exceeded expectations. I have not found any source of light which approaches it in intensity, and, except for the wearing of the protective goggles, gives as much ease of manipulation and is as free from objectionable features. Speed of exposure, which is a necessary factor for good photographs, is assured with the lamp. The lens may be stopped down, which aids in giving depth to the picture. There is no attendant explosion, and no smoke to upset the office or to make further stay in the room impossible for more pictures or other purposes. (If a smoke bag is used, light is cut down.)

As far as I know, the mercury quartz lamp has not previously been delegated for such lowly function. Perhaps others may find that it solves their lighting problem for clinical photographs.

HERMAN GOODMAN, M.D., New York.

Abstracts from Current Literature

TUBING AS A CAUSE OF REACTION TO INTRAVENOUS INJECTION, ESPECIALLY OF ARSPHENAMIN. JOHN H. STOKES and G. J. BUSMAN, J. A. M. A. **74**:15 (April 10) 1920.

The writers investigated the cause of an arsphenamin reaction, characterized by a chill with a sharp rise in temperature coming on from thirty minutes to one hour after intravenous injection, accompanied by nausea, vomiting, diarrhea, pain in the head and back and varying degrees of prostration. This reaction appeared in crops, so to speak, and then disappeared for a considerable period, only to recur in the midst of what appeared to be a period of flawless technical accuracy.

It was finally determined that this reaction resulted from the employment of a certain widely distributed brand of so-called pure gum rubber tubing. The tubing, when new, appears to contain a toxic agent responsible for the reaction. The toxic substance gradually disappears from the tubing on use, and may be removed in the first instance by soaking the tubing for six hours in normal sodium hydroxid solution and rinsing. The toxic property is not destroyed in the ordinary process of sterilization by boiling (from one-half to one hour), is not soluble in water or removable by irrigation, appears in toxic amounts in arsphenamin, neo-arsphenamin and dilute sodium hydroxid solution merely on passing them through a new tube en route from container to vein, and apparently is not associated with the mechanically removable debris from the inner surface of the tube.

LEVIN, New York.

THE FREQUENCY WITH WHICH VARIOUS LOCALITIES ARE ATTACKED BY LUPUS VULGARIS. CARL WITH, Brit. J. Dermat. & Syph. **32**:287, 1920.

Compiling statistics from 897 cases of lupus vulgaris, in which 665 patients were above 16 years of age, 116 between the ages of 11 and 16, and 116 below 11 years of age, With gives the frequency of lupus in various sites at various age periods. His findings confirm the old observations regarding the frequency of lupus on and in the nose, the way in which one attack depends on the other, and regarding the lymphoma on the neck playing the greatest rôle for the lupus in that site. It has been demonstrated that lupus on and in the nose, compared with lupus on the center of the cheek, is comparatively rare in children, but increases between the ages of 11 and 16; and the comparative frequency of lupus on the extremities during childhood is confirmed.

SENEAR, Chicago.

EYE LESIONS PRODUCED BY LIGHT RICH IN ULTRAVIOLET RAYS. J. VAN DER HOEVE, Am. J. Ophth. **3**:178 (March) 1920.

The writer states that nearly every part of the eye is susceptible to damage by undue exposure to natural or artificial light rich in ultraviolet rays. The cornea and lens in particular show a selective absorption for these rays and whether the superficial or deep parts of the eye are affected depends on

the wave length of the rays, those of shorter wave length being more readily absorbed. The most frequent affection is photophthalmia, characterized by intense photophobia and lacrimation with sometimes blepharospasm and ciliary neuralgia. Other conditions are acute conjunctivitis, iritis and keratitis, senile cataract and senile degeneration of the macula. Snow blindness is cited as an affection of this character due to natural light rich in ultraviolet rays, while as artificial causative agents are mentioned the mercury vapor lamp, arc lamp, electric welding and short circuit flashes. The writer does not consider short therapeutic exposures with the Kromayer mercury vapor lamp as distinctly harmful, especially when the pupillary part is not directly exposed.

CULTURAL STUDIES ON A CASE OF SPRUE. WADE W. OLIVER, J. A. M. A. **74**:27 (Jan. 3) 1920.

Oliver reports laboratory studies on a case of sprue—that of an American invalided to Brooklyn from Porto Rico:

From the stool, from tongue scrapings, from sputum and from tooth abscess, a growth of yeasts was obtained which corresponded in the main to *Monilia psilosis*, described by Ashford as the cause of sprue.

Morphology.—The yeast exhibited a striking variation in size and form, which seemed somewhat independent of the medium, as a mount made from a single colony showed a polymorphinism among its members. The single cells were round or oval, varying in diameter from about 2 to 7 microns, were sharply defined in outline, and possessed a nucleus which was recognizable in fresh preparations. Many cells showed an oval or spherical, faintly outlined vacuole. Mycelial elements were constantly observed in + 1 glucose agar but best apparently in gelatin.

A guinea-pig was inoculated with an agar culture of this organism. Death occurred in seven days Postmortem examination revealed a large abdominal abscess involving various organs.

From the gall bladder, as well as from a liver abscess, *Monilia* was recovered in culture mixed with *Staphylococcus aureus*.

CLARK, Chicago.

DERMATITIS DUE TO CARPOGLYPHUS PASSULARUM. W. J. O'DONOVAN, Brit. J. Dermat. & Syph. **32**:297, 1920.

O'Donovan reports the case of a man who, while shoveling dried figs, developed over the forearms, backs of the hands and on the face an eruption of discrete, closely set, apparently follicular papules, pale pink in color with red scabbed tops. The lesions were suggestive of scabis, but were too small, and there was no evidence of burrowing.

Examination of the figs showed them to be covered with a fine, light brown powder, which microscopic examination disclosed was made up of live and dead mites and numerous fragmented particles of acari and their limbs. The parasite was identified as *Carpoglyphus passularum*. The author states that Rasch had previously described two cases of dermatitis due to the Carpoglyphus occurring among workers who had been handling dried plums.

SENEAR, Chicago.

CASE OF ACUTE LUPUS ERYTHEMATOSUS. E. G. GRAHAM LITTLE, Proc. Roy. Soc. **2**:3 (Sept.) 1920.

A case report.

GUY, Pittsburgh.

RADIUM IN THE TREATMENT OF DISEASES OF THE EYE AND ADNEXA. G. B. New and W. L. Benedict, Am. J. Ophth. **3**:245 (April) 1920

The writer's observations were drawn from a series of 133 cases, of which ninety-seven were basal cell epitheliomas of the lids and canthus. Radium was used in the unscreened plaque and silver tube without additional screening other than rubber tissue. The dosage was uniformly heavy for the malignant lesions and in many cases it was carried out over a period of several days. Five case reports were submitted in which the dosage and mode of application were definitely stated. Blastomycosis, vernal catarrh and the angiomas were among the lesions considered favorable for radiotherapy. The thorough use of the knife or cautery preceding the application of radium was advised for melanotic sarcoma, glioma, squamous cell epithelioma, and those cases of basal cell epitheliomas infiltrating deep tissues or involving bone.

UEBER ZWEI FALLE VON NEURODERMITIS NODULOSA (GROSZNOTIGE FORM DER NEURODERMITIS BROCQ) (TWO CASES OF NEURODERMITIS NODULOSA). J. Fabry, Arch. f. Dermat. u. Syph. **121**:241 (April) 1915.

Two cases are reported. The first one was described by the author in 1895 as urticaria papulosa perstans. Now, after many years of study, he believes the case is one of neurodermitis of Brocq.

The lesions were pigmented papules about 0.5 cm. in diameter, with a thin scale. New lesions were red while the old ones were dark gray in color. There was leather-like thickening with lichenification. The entire skin was of a grayish color. There was no tendency to urticarial lesions. The patients suffered with intense persistent itching. Treatment was of no avail.

Heithaus, Cleveland.

CLINICAL NOTE. CHRYSAROBIN AS A CAUSE FOR PSORIASIS. E. Ward, Brit. J. Dermat. & Syph. **32**:299, 1920.

Ward cites a case in which a man who had used chrysarobin ointment successfully for many years in the treatment of psoriasis, doubled the strength of the ointment. The lesion cleared up in the usual way, but fresh papules appeared in a circle at the inner margin of the red zone produced by the treatment. A milder chrysarobin ointment removed the new papules successfully.

Senear, Chicago.

REPORT OF A CASE OF GENERALIZED PSORIASIS AND AMENORRHEA CURED WITH OVARIAN EXTRACT. G. Verrotti, Riforma med. **36**:321, 1920.

Verrotti reports the case of a woman, 29 years old, who for six years had been suffering from a stubborn psoriatic eruption. Her menses had been scanty since the beginning of the dermatosis and had finally disappeared entirely. In spite of all kinds of local treatment, the disease remained practically unchanged until the author decided to give the patient ovarian extract. The eruption vanished in a short time, menstruation returned and the patient has remained well for eighteen months.

Pardo-Castello, Havana.

DES FORMES ABORTIVES DE LA MALADIE DE RECKLINGHAUSEN (THE ABORTIVE TYPES OF RECKLINGHAUSEN'S DISEASE). C. ADRIAN and G. HÜGEL, Ann. de dermat. et syph. **7**:152 (May) 1919.

Adrian and Hügel report two cases of the disease with irregular disseminated patches of pigmentation, without tumors and nerve involvement. One of the patients subsequently developed about a dozen tumors the size of peas, situated on the chest and thighs.

BECHET, New York.

LES LOCALIZATIONS HORS DES PLIS DE L'EPIDERMOPHYTON INGUINALE (THE LOCALIZATION OF THE EPIDERMOPHYTON INGUINALE, OTHER THAN IN THE FOLDS). PAUTRIER, Ann. de dermat. et syph. **7**:278 (Sept.) 1919.

The author reports two cases of eczema marginatum, with lesions scattered over the legs and trunk, in which *Epidermophyton inguinale* was demonstrable.

BECHET, New York.

SPECIALE COMPORTAMENTO DEL LIQUIDO CEFALO-RACHIDIANO NELLA NEUROSIFILIDE PER LA PRESENZA DI ANTICORPI SPECIFICI TERMOLABILE (BEHAVIOR OF THE SPINAL FLUID IN SYPHILIS OF THE NERVOUS SYSTEM DUE TO THE PRESENCE OF THERMOLABILE SPECIFIC ANTIBODIES). C. RIZZO, Lo Sperimentale **74**:1 (January-June) 1920.

The author reports that in his experience the spinal fluid inactivated at a temperature of 56 C. may give a negative Wassermann reaction, while if used active, it gives a positive test. He says that the spinal fluid should never be inactivated, as it contains thermolabile specific antibodies which are destroyed by heat.

PARDO-CASTELLO, Havana.

STIGMATA OF PREDISPOSITION TO BONE AND JOINT TUBERCLE. W. C. RIVERS, Brit. J. Child. Dis. **199-201**:140 (July-Sept.) 1920.

English schoolchildren were the objects of this investigation. As a result of observations in 353 tuberculous cases as compared with 610 normal controls, it was concluded that in bone and joint tuberculosis red and reddish hair is nearly twice as frequent as in the ordinary population (7 per cent. as compared with 3.4 per cent.). Probably also a tendency to permanent freckling is a little commoner in those with bone and joint tuberculosis than in normal children. Again, in 421 cases, contrasted with 324 "controls," it was found that ichthyosis is seen at least twice as frequently in afflicted as in nontuberculous children. In view of the possible atavistic nature of red hair and ichthyosis, these findings are of interest.

PARKHURST, New York.

HEREDITARY SYPHILITIC AORTITIS. E. J. STOLKIND, Brit. J. Child. Dis. **199-201**:126 (July-Sept.) 1920.

In a search of the literature the author has been unable to find any cases in which *Spirochaeta pallida* has been found in the aorta of children with

hereditary syphilis, aged more than 1 year. Authors so far are not agreed as to the typical pathologic changes of hereditary syphilis in the aorta of fetuses and new-born infants, and this question needs further investigation. On the other hand, the lesions of syphilitic aortitis in adolescents and adults are characteristic. There is given a brief outline of the cases of alleged hereditary syphilitic aortitis, with the author's conclusion that he has so far been unable to find in the literature a single case of proved hereditary syphilitic aortitis, though such cases may exist. Further researches are needed.

PARKHURST, New York.

UN CAS DE DERMATITE DE DUHRING PUSTULEUSE (A CASE OF DUHRING'S DISEASE WITH PUSTULAR LESIONS). MILIAN, Ann. de dermat. et syph. **7**:193 (July) 1919.

The author comments on the rarity of primary pustular lesions in dermatitis herpetiformis, and reports an example of this particular type of eruption.

BECHET, New York.

UEBER MANIFESTATIONEM DER LUES AM AUGE BEI POSITIVEM LIQUORBEFUND (MANIFESTATIONS IN THE EYE OF SYPHILITIC PATIENTS WITH POSITIVE FINDINGS IN THE CEREBROSPINAL FLUID). L. STROSS and A. FUCHS, Wien. klin. Wchnschr. **33**:986, 1920.

The authors undertook to study the eye in all cases from Kyrle's clinic in which there were positive findings in the spinal fluid. They tabulate the findings:

POSITIVE CEREBROSPINAL FLUID FINDINGS

	Men	Women	Total
Early syphilis, positive eye findings....	6	11	17
Early syphilis, negative eye findings...	14	18	32
Late syphilis, positive eye findings.....	12	7	19
Late syphilis, negative eye findings.....	9	7	16

The relative involvement of the eye in the early and late cases, and in men and women may be learned from this table.

No attempt is made to formulate percentage tables, etc., because only by long continued studies over long periods of time will the relationship between positive findings in the spinal fluid of syphilitic patients and disease of the eye be fully understood.

GOODMAN, New York.

REVIEW OF UNTOWARD EFFECTS FOLLOWING ARSPHENAMIN AND ITS DERIVATIVES. W. P. BOARDMAN, Boston M. & S. J. **183**: 561 (Nov. 11) 1920.

The author reviews recent literature on the subject, citing two fatal cases, one from exfoliative dermatitis and the other from acute yellow atrophy of the liver. Various complications are discussed in more or less detail, as well as certain of the contraindications.

LANE, Boston.

CHRONIC FIBROID SUBCUTANEOUS SYPHILOMATA OF THE LEGS, ASSOCIATED WITH CHRONIC PERI-URETHRAL INDURATION IN THE PENIS. F. PARKES WEBER, Proc. Roy. Soc. Med. **13**:9 (July) 1920.

Multiple subcutaneous painless hard nodules on the legs below the knees, with one similar lesion on the outer side of the right thigh and another in the distal half of the penis, in a patient with a positive Wassermann reaction, were found to be composed of masses of fibrous tissue with numerous foci of chronic inflammation. The condition was little affected by specific therapy or fibrolysin. In a discussion Dr. McDonagh spoke of the condition as "induratio penis plastica," which he stated was never due to syphilis, but in over 50 per cent. of cases it was associated with glycosuria or hyperglycemia. He ascribed the condition to "acidness" of the blood and stated that in early cases colloidal iodin and intramin would bring about its dissolution.

GUY, Pittsburgh.

RADIUM IN DERMATOLOGIC PRACTICE. LOUIS B. MOUNT, Urol. & Cutan. Rev. **24**:10 (Oct.) 1920.

The greatest use of radium is in epithelioma of the skin. Healing is obtained with slight inconvenience to the patient, no discomfort of any moment, and with cosmetic results unobtainable by any other means. Other cutaneous conditions in which it is recommended are: keloids and keloidal scars, acne keloid, keratoses and preepitheliomatous lesions, plantar warts, verrucae and papillomas, chronic eczema, lymphangioma circumscriptum, lupus vulgaris, lupus erythematosus and cheilitis exfoliativa.

LEVIN, New York.

THE PREPARATION OF AMBOCEPTOR WITH HUMAN ERYTHROCYTES. A. H. SANFORD, Am. J. Syph. **4**:697 (Oct.) 1920.

The author employed the human erythrocytic hemolytic system and found that its chief disadvantage, that is, removal of the natural hemagglutinins from the amboceptor, may be eliminated by using dogs for developing the amboceptor. Small dogs are most suitable. From 30 to 60 c.c. of a 50 per cent. suspension are injected intraperitoneally at intervals of one week. From 3 to 5 injections are required.

The amboceptor obtained has a comparatively low titer, averaging about 1 : 500.

TOMLINSON, Omaha.

CASE OF 1. LUPUS ERYTHEMATOSUS (ANOMALOUS TYPE). 2. FOLLICULITIS ULERYTHEMATOSA RETICULATA OF McKEE. H. C. SAMUEL, Proc. Roy. Soc. **2**:3 (Sept.) 1920.

1. Lupus erythematosus or folliculitis ulerythematosa of McKee. This case exhibited telangiectases followed by superficial scarring in the form of reticulate pitting and affecting the flush areas of the face. A family history of tuberculosis was noted, and the patient had an evident weak circulation. The age of the patient (34) and absence of comedones were considered against the second diagnosis.

GUY, Pittsburgh.

FUNKTIONSSTOERUNGEN DES SYMPATIKUS. KRIESSAERTZLICH-DERMATOLOGISCHE BEOBACHTUNGEN (DISTURBANCE OF THE FUNCTION OF THE SYMPATHETIC. WAR OBSERVATIONS IN DERMATOLOGY). Oscar Sprinz, Arch. f. Dermat. u. Syph. **123**:894, 1916.

In this article the author gives a review, and recounts his personal experience with dermatologic diseases following injury from war wounds to the sympathetic nervous system. Addison's disease, herpes zoster gangrenosus, hypertrichosis, and disturbances of the pilomotor and secretory functions of the skin have followed injuries to the sympathetic nervous system. Changes in nail growth are also mentioned.

Goodman, New York.

LUES UND KARZINOM (SYPHILIS AND CARCINOMA). Gustav Stümpke, Arch. f. Dermat. u. Syph. **123**:1082, 1916.

Stümpke adds a case of a relationship between syphilis and carcinoma to those already well known. He mentions the existence of carcinoma on the basis of late skin manifestations of syphilis, on scars, on the site of chancre and on leukoplakial degeneration.

The case history given is not convincing.

Goodman, New York.

A STANDARDIZED METHOD OF PERFORMING THE WASSERMANN REACTION. William A. Hinton, Am. J. Syph. **4**:598 (Oct.) 1920.

The author reports a standardized method for performing the Wassermann reaction which has been quite generally adopted in Massachusetts. He gives a detailed description of his technic, including the preparation of all materials used.

Tomlinson, Omaha.

CHOLESTERINEMIA AND THE WASSERMANN REACTION. Edwin Henes, Jr., Am. J. Syph. **4**:685 (Oct.) 1920.

On account of the varying degrees of cholesterinemia found in different patients, the author does not consider a cholesterinized antigen reliable unless the cholesterin content of the blood has been determined. He considers it important to determine the cholesterin content of the blood if we are to obtain reliable Wassermann reactions.

Tomlinson, Omaha.

UEBER ZWEI FAELLE VON CONJUNCTIVO-KERATITIS GONORRHOICA (TWO CASES OF CONJUNCTIVO-KERATITIS GONORRHOICA). J. W. Van der Valk, Acta Dermat.-Vener. **1**:254 (Oct.) 1920.

The differences between the parakeratotic papule of gonorrhea and the erosive lesions under the prepuce and on the eye are probably due solely to their great differences in moisture and protection.

Reviewing the literature concerning the mode of origin of these lesions, the author concludes that, instead of being blood borne, it is quite possible that the causative agent, be it organism or toxin, may follow the nerve fibrils. The corneal distribution of the condition in his two cases suggested this.

Parkhurst, New York.

CASE OF CHRONIC DIPHTHERITIC GRANULOMA. F. G. GRAHAM LITTLE, Proc. Roy. Soc. **2**:3 (Sept.) 1920.

An officer serving in France developed medallion-like lesions, with warty centers and ulcerating edges, on the right side of the right foot, the dorsum of the toes of the left foot, on the left shoulder and at the orifice of the left nostril. The hard palate and the fauces were similarly affected. An organism closely resembling the Klebs-Loeffler bacillus was found, but on account of the fact that the patient had had several attacks of gonorrhea the possibility of a gonorrheal hyperkeratosis was considered, this being considered unlikely on account of the mucous membrane involvement.

GUY, Pittsburgh.

UEBER DAS VERHALTEN DER WASSERMANNSCHEN REAKTION BEI TUBERKULIDEN (CONCERNING THE POSITION OF THE WASSERMANN REACTION IN TUBERCULIDS). OTTO SACHS, Arch. f. Dermat. u. Syph. **123**:838, 1916.

The Wassermann reaction has been reported positive in a number of cases of tuberculid, and Sachs has had two cases. Other cases of tuberculid have given the negative reaction. One must make a careful inquiry into the antecedent history for the possibility of syphilitic infection, as well as make a complete physical examination. Only after a long study of many clinical cases will any worthy conclusions be reached. The effort will not only add to the significance of the tuberculids, but it is necessary to maintain the position of the Wassermann reaction.

GOODMAN, New York.

THE DIAGNOSIS OF PRIMARY SYPHILIS. H. D. LLOYD, Boston M. & S. J. **183**:540 (Nov. 4) 1920.

A discussion of the clinical, dark-field and serologic diagnosis of early syphilis is presented. The author emphasizes the early use of the dark-field examination, quoting a series in which a positive diagnosis was made in 96 per cent. of the cases by means of the dark field.

LANE, Boston.

A CASE OF DELHI BOIL OR SORE. J. H. STOWERS, Brit. J. Dermat. & Syph. **32**:263 (Aug.-Sept.) 1920.

As a clinical note, Stowers reports a case of Delhi boil seen in England. The patient, a woman aged 34 years, had resided in India for the past nine years. There were two nodules below the right eye, and a third on the left forearm. The parasite, *Leishmania tropica*, was easily demonstrated by Dr. Castellani.

SENEAR, Chicago.

DIE THERAPEUTISCHE ANWENDUNG DER KUENSTLICHEN HOEHENSONNE IN DER DERMATOLOGIE (THE THERAPEUTIC APPLICATION OF THE ARTIFICIAL SUN LAMP IN DERMATOLOGY). G. SCHERBER, Arch. f. Dermat. u. Syph. **123**:843, 1916.

Pemphigus vulgaris, dermatitis herpetiformis, chronic granulating wounds, ulcers of tuberculosis, ulcers of the leg, lichen rubra acuminatus, prurigo and

scleroderma have been distinctly benefited by the use of the artificial sun rays. The treatment is of greatest benefit if used in conjunction with other means of therapy, for example, arsenic, tuberculin injections and other therapeutic measures, as indicated.

GOODMAN, New York.

THE PREVENTION OF VENEREAL DISEASE BY IMMEDIATE SELF-DISINFECTION. H. WANSEY BAYLY, Internat. J. Surg. **33**:213 (July) 1920.

The author believes that failure of disinfection methods is due to lack of proper material and knowledge of its use rather than to the antiseptics themselves. This method also is of much less value to women than to men. The author favors venereal prophylaxis for both men and women at the earliest possible moment after exposure, using 33 per cent. calomel ointment and 1:1,000 potassium permanganate.

JAMIESON, Detroit.

CONSERVATION DU REFLEXE OCULO-CARDIAQUE DANS L'HEREDO SYPHILIS MEME COMPLIQUEE D'AORTITE. AVEC UNE OBSERVATION D'INSUFFISANCE AORTIQUE TRAUMATIQUE CHEZ UN HEREDO-SYPHILITIQUE (CONSERVATION OF THE OCULOCARDIAC REFLEX IN TRUE HEREDO-SYPHILIS COMPLICATED WITH AN AORTITIS. REPORT OF A CASE OF TRAUMATIC AORTIC INSUFFICIENCY IN A HEREDOSYPHILITIC). MOUGEOT, Ann. de dermat. et syph. **7**:157 (May) 1919.

Mougeot concludes from a study of the subject that the oculocardiac reflex in a large majority of cases of hereditary syphilis remains intact. It is absent in one half of the cases of acquired secondary syphilis, and in four fifths of the cases of tertiary syphilis without demonstrable nervous involvement. It is almost entirely absent in cerebrospinal syphilis.

BECHET, New York.

DIE PUNKTION DES RUECKENMARKKANALES (LUMBALPUNKTION) IN DER DIAGNOSE UND THERAPIE DER SYPHILIS (LUMBAR PUNCTURE IN THE DIAGNOSIS AND TREATMENT OF SYPHILIS). CARL STERN, Arch. f. Dermat. u. Syph. **123**:943, 1916.

This monograph of about 120 pages deals with the history of lumbar puncture, the anatomy of the parts involved, the technic of the operation and studies of the normal and abnormal fluids. There is a critical analysis of the literature on cell counting, the origin of the cells in the fluid, the Nonne-Apelt Phase 1 reaction, globulin, the colloidal gold reaction of Lange, the Wassermann reaction and its significance, pathologic anatomy of early syphilitic meningitis, clinical relation to fluid findings, death following puncture, technic and results of intraspinal arsphenamin and the demonstration of spirochetes in the fluid. A statistical summary of the reported lumbar punctures and conclusions reached by a study of about 1,200 studies on the fluid (200 personal cases) closes the paper. The conclusions are those of 1916, and are of historical interest. The bibliography occupies five closely printed pages.

GOODMAN, New York.

YPERITES GENITALES SIMULANT LA SYPHILIS, ET SYPHILIS MASQUEE PAR YPERITE (YPERITE GAS BURNS OF THE GENITALIA SIMULATING SYPHILIS AND MASKED SYPHILIS FROM YPERITE BURNS). GOUGEROT and CLARA, Ann. d. mal. vénér. **14**:258 (May) 1919.

The authors state that gas burns of the genital region alone, or as a part of a general burn, had frequently been observed by them. The lesions frequently simulated primary syphilis, and occasionally masked the beginning of syphilis. The burns often cause an extensive phimosis or paraphimosis, with subpreputial inflammation and induration of the inguinal glands. Evolution alone eliminates the possibility of an associated syphilis. The authors report a number of cases.

BECHET, New York.

THE TREATMENT OF BILHARZIASIS WITH ANTIMONY. J. E. R. MCDONOUGH, J. Trop. M. **23**:165 (July 1) 1920.

The author has found tartar emetic to be the best drug for intravenous use, having it prepared in ampules containing 1 c.c. of distilled water and 1½ grains of the drug. The contents are diluted up to 100 c.c. before injection. Injections are repeated every five days for ten doses.

JAMIESON, Detroit.

THE DEVELOPMENT OF COSMETIC RHINOPLASTY. SEYMOUR OPPENHEIMER, New York State J. M. **20**:355, 1920.

The author refers to various surgeons who, from the earliest times, have undertaken this operation, and pleads for the recognition of rhinoplasty as a legitimate and often necessary procedure. There is no discussion of technic or results.

WILLIAMS, New York.

PROGNOSTIC DES CHANCRES EXTRA-GENITAUX (THE PROGNOSIS OF EXTRA-GENITAL CHANCRES). DUJARDIN, Ann. de dermat. et syph. **7**:221 (July) 1919.

The author concludes from a study of fifty-three extragenital chancres that the prognosis in no way differs from the genital chancre, thereby corroborating Fournier's dictum.

BECHET, New York.

LES ARHYTHMIES DE LA SYPHILIS SECONDAIRE (THE ARRHYTHMIAS IN SECONDARY SYPHILIS). DUCASTEL, Ann. d. mal. vénér. **14**:263 (May) 1919.

DuCastel states that he has frequently observed, both by touch and sphygmograph, irregularity of the pulse in secondary syphilis. Tachycardia was not frequent; only fifteen of fifty syphilitic patients had a pulse beat higher than 90. Arterial tension was below normal. In patients suffering from tachycardia, the pulse was soft, compressible and dicrotic. There was some precordial distress. He concludes that the arrhythmias in secondary syphilis have no grave significance, and almost invariably disappear in time.

BECHET, New York.

SURGICAL ASPECTS OF THE CHARCOT JOINT AND OTHER SYPHILITIC BONE AND JOINT LESIONS. FREDERIC J. COTTON, Ann. Surg. **72**:488 (Oct.) 1920.

The poor results usually experienced in the surgical treatment of charcot joints is probably due to their being handled as a purely surgical condition without due regard to the syphilitic element.

The author, in reporting results in his cases, recommends active antisyphilitic treatment prior to surgical measures.

TOMLINSON, Omaha.

DIE KUTIREAKTION BEI LEPRA UND IHRE BEZIEHUNG ZUM LEPRAERYSIPELOID (DERMAL REACTION IN LEPROSY AND ITS APPLICATION TO ERYSIPELOID ATTACKS IN LEPROSY). ROBERT OTTO STEIN, Arch. f. Dermat. u. Syph. **123**:908, 1916.

Stein utilized lymph nodes from a lethal case of leprosy to make an antigen which he used for an intradermal test for the disease. Positive reactions were secured in cases of leprosy that showed erysipeloid attacks. Stein thinks that malignant syphilis among syphilitics, papulonecrotic tuberculids among the tuberculous, and erysipeloid attacks among the lepers are analogous results of a hypersensitiveness to the causative virus.

GOODMAN, New York.

LICHEN PLANUS. S. E. DORE, Proc. Roy. Soc. **2**:3 (Sept.) 1920.

A woman, aged 43, had two patches on the shins composed of closely set, acuminate, hard papules on a thickened skin, which was sepia colored. At the margins, the papules, which were not follicular, were arranged in rows.

GUY, Pittsburgh.

LA QUESTION DES APPAREILS DE VERRE DANS LES ACCIDENTS DU NEO-SALVARSAN (THE ROLE PLAYED BY GLASSWARE IN THE ETIOLOGY OF NEO-ARSPHENAMIN ACCIDENTS). J. GOLAY, Ann. de dermat, et syph. **7**:299 (Sept.) 1919.

The author is convinced that a small amount of neo-arsphenamin solution remains adherent to the glassware in spite of repeated washing, sterilization and disinfection. A part of this old oxidized neo-arsphenamin is taken up in solution at the next injection, thereby causing grave accidents. Golay, therefore, recommends repeated washings, and the testing of the washings with a 2 per cent. or 4 per cent. solution of silver nitrate. In the presence of even the minutest particles of arsenic there is a blackish or violaceous brown precipitate. The reaction is one of great delicacy, occurring in a solution of neo-arsphenamin as weak as one part in 100,000,000.

BECHET, New York.

SURGICAL TREATMENT OF ULCUS TROPICUM. ROBERT HOWARD, J. Trop. M. **23**:215 (Sept. 1) 1920.

Thorough curetting and removal of the undermined edge are recommended as the method of choice in treating this condition.

JAMIESON, Detroit.

DERMATOLOGIC ABSTRACTS

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

GASTRIC ANALYSIS IN ACNE ROSACEA. J. A. RYLE and H. W. BARBER, Lancet **2**:1195, 1920.

A number of cases of acne rosacea were examined by Ryle and Barger with a view to determining, if possible, the actual pathogenesis of the condition and the most satisfactory method of treatment. The connection between this disease and dyspnea is generally recognized, and it is usually supposed that overindulgence in alcohol, tea, or coffee produces its effect by setting up a chronic gastritis. Twelve cases of acne rosacea were investigated by the fractional method of gastric analysis. In five there was complete achlorhydria throughout the period of the meal. In two cases there was an extreme degree of hypochlorhydria. Of the remaining five cases, one showed no secretion of free hydrochloric until after one hour, and two showed a temporary high peak in the curve of acidity, with an abrupt fall to the base line. Other features revealed by the test were a tendency to rapid emptying, such as obtains in other cases of so-called achylia gastrica, and a highly mucoid resting secretion, frequently of the viscid consistency of raw eggwhite. The increased liability to acne rosacea during menstrual period and pregnancy is of interest, in view of the fact that achylia is also reputed to be more common at these times. The administration of dilute hydrochloric acid, 30 minutes and upward, well diluted, after meals or during meals, has yielded very satisfactory results.

Society Transactions

NEW YORK DERMATOLOGICAL SOCIETY

Regular Meeting, Nov. 23, 1929

JAMES McF. WINFIELD, M.D., *President*

ACNITIS. Presented by DR. WINFIELD.

A young man, aged 20, was always healthy until May, 1920, when he had an attack of appendicitis. He was ill for nearly a month. The appendix was not removed; the treatment consisted of application of ice bags. On recovery he noticed a number of small papules scattered over the nose, forehead and chin; some of them enlarged and broken down, which on healing left scars. The patient stated he had never had any previous skin eruption, such as acne or comedones. When Dr. Winfield first saw the patient there were a great many acne-like lesions scattered over the face and scalp. Some of them on the face resembled molluscum contagiosum; many of the papules had ulcerations; all had left scars. Those over the scalp and bearded portions of the face were accompanied by loss of hair. In addition to the papules, there were a number of deep seated nodules, especially about the neck. The case was shown because the acnitis had followed an attack of appendicitis in a subject who had always been in perfect health. The Wassermann test was negative, as was the tuberculin test.

The young man was of slender build and rather narrow chested. He had not been passed by the army examining board on account of questionable signs in the chest, although at present nothing was found on physical examination. Dr. Winfield was inclined to think the tuberculous focus was in the appendix.

DISCUSSION

DR. TRIMBLE agreed with the diagnosis. He had seen the patient previously in consultation. At that time he presented the exact picture shown at present, though there were many small lesions and hardly any large ones.

The case semed to belong to the category of Barthélemy's acnitis, one of the synonyms of necrotic granuloma. He had been much interested in the history which showed that the condition followed an attack of appendicitis.

CASE FOR DIAGNOSIS. (MYCOSIS FUNGOIDES, LEUKEMIA CUTIS, IDIOPATHIC ATROPHY, ACRODERMATITIS ATROPHICANS?) Presented by DR. LANE.

The patient, A. B., was a man 45 years of age. He had always been well until the present trouble started, except for a "weeping eczema" of the hands, which had recurred chiefly during the summer time, from 1893 to 1914. This had been absent since that time. The present trouble started in 1907 as dry itching spots on the elbows and shins. It had gradually progressed.

Over both elbows the skin was red, wrinkled and atrophic. The legs and the lower half of the thighs were covered with a reddened, somewhat thickened skin. In some areas there was slight lichenification and numerous excoriations due to scratching. In some areas, especially on the thighs, at the upper and outer borders of the eruption, there were elevated, urticaria-like spots. Such spots appeared, according to the statement of the patient, every three or four weeks. Their appearance was usually preceded by a short period of malaise with slight elevation of temperature. After about a week they usually disappeared, as did the intense pruritus with which they were attended.

The patient had been seen once only, and it had been impossible to compiete the necessary examinations in time for presentation, but the results of these examinations would be stated later.

DISCUSSION

DR. WISE was of the opinion that the lesions were not those of mycosis fungoides, or leukemia cutis, or lymphogranulomatosis cutis, or any of the diseases grouped under the leukemias. He believed the condition more likely to be an atypical form of atrophoderma.

DR. POTTER did not care to make a diagnosis before studying the case carefully.

DR. WINFIELD said that from the imperfect examination, he was inclined to consider the case one of mycosis fungoides. The intense itching, the adenopathy and the tumefaction of some of the lesions, all pointed to that diagnosis.

DR. TRIMBLE said that it was difficult to foresee how these chronic conditions would develop. They not infrequently became transformed into other conditions after continuing from year to year. Just now the condition resembled mycosis gungoides more than any other condition, but if it was not that, it was one of those skin conditions associated with leukemia. The amount of infiltration would lead one away from the diagnosis of idiopathic atrophy. The only lesion on the patient he could reconcile with that diagnosis was the one on the elbow; there was a crinkled condition there that looked as though it might thin out and be termed cigaret-paper skin.

DR. HIGHMAN said that from the fact that the lesions were mainly on the lower half of the body, as well as the itching, the infiltration, the color and the general adenopathy, one would expect the condition to be either mycosis fungoides or leukemia. He was inclined to think it more likely to be leukemia than mycosis fungoides, but this would be revealed only by further study. He would not be surprised at the atrophy in either of these two conditions, as Dr. Wise had himself described it. The dermatoses do sometimes lead to atrophy of the skin, and there seemed to be little doubt that the case belonged to this group.

DR. MACKEE expressed the opinion that the case was either mycosis fungoides or leukemia, for the reasons already stated by the previous speakers.

DR. WISE inquired how long the condition had lasted, and on being told that the duration was six years, he asked whether one could have a leukemia for six years and show no serious constitutional changes.

ALOPECIA AREATA TOTALIS. Presented by DR. WISE for DR. FORDYCE.

A boy, aged 3, exhibited a total loss of hair, including that of the eyebrows, eyelashes and scalp. The duration of the condition was two years. The intention was to present the father and son, both of whom presented total alopecia.

DERMATITIS FACTITIA. Presented by Dr. Howard Fox.

N. McD., a girl, 23 years of age, born in the United States, who had been employed at different times as a domestic and as a factory worker, whose family history, as far as obtainable, was negative, as a child had been operated on for a cleft palate. She was a poor student, and had left school at an early age. She had suffered from two attacks of appendicitis and from frequent colds. She had always been very nervous, and had recently suffered from "bladder trouble," occasionally requiring to be catheterized. The menses were established at 15, and had since been very irregular, the flow being slight and the pain severe.

During the past six years she had suffered from a long and varied list of accidents, each of which, according to her statement, resulted in the deforming scars which she presented. There was one deep, sharply circumscribed ulceration on the wrist and numerous scars on the forearms and other parts of the body accessible to the hands. They varied in size and shape, many of them having a distinctly artificial appearance. They were entirely too extensive and deforming to have been the result of ordinary trauma. The accidents which she recounted in detail as the cause of the individual lesions were trivial in many cases, such as a scratch, mosquito bite, venesection, slipping on a stone while bathing, etc. There was invariably an interval of several weeks between the trauma and resulting ulceration which appeared suddenly and required from one to six months to heal. There was complete absence of the corneal reflex and other stigmas of hysteria.

The diagnosis was accepted without dissent.

DISCUSSION

Dr. MacKee said that these cases are always exceedingly interesting, and one cannot see too many of them. He then cited the case of a girl who, after an appendectomy, left the hospital with the wound doing very well, but it ceased to heal and became keloidal, and was then treated with the roentgen rays. The keloid disappeared, but the wound opened again and refused to heal. It turned out to be a case of dermatitis factitia. She kept digging in the wound, and after a sealed dressing was used she stained the gauze with menstrual discharge. The number of artifices she used to fool the physician was remarkable. The wound healed with a plaster dressing. Every time the dressing was not used the wound would open.

Dr. Winfield said he had been interested in the ulcerations, and the various things that are used by these patients to keep the wounds open. He thought the agent used in this case was caustic soda. There was always necrotic tissue when phenol was used. Caustic soda made a clean cut ulceration.

Dr. Howard Fox said he had not attempted to induce the patient to tell the means that she had used in her self-mutilation. As malingering had been suspected, her physician had put a plaster cast on the arm. It was removed at her request at the end of three weeks as she complained of severe pain. Deep ulcerations were found at both upper and lower ends of the cast, but none on the parts that had not been accessible to her hands.

FOR DIAGNOSIS. Presented by Dr. Trimble for Dr. Rothwell.

A white woman, German, 49 years old, presented a circinate arrangement of small, soft nodules, one-sixteenth or one-eighth inch in diameter, about the

tip of the nose, with small spots of superficial scarring evident in the area of the patch which had a diameter of about one-half inch. The color of these nodules was reddish-yellow or brownish-red, suggestive of the apple-jelly color of lupus nodules, and they were about six or eight in number.

The history given was that the condition was of about seven years' duration altogether, disappearing after courses of injection of mercury and mouth administration of potassium iodid, and reappearing some time after the discontinuance of such treatment. Various Wassermann reactions were negative; none was positive. There was no history of a syphilitic nature. Another blood specimen was taken four days before presentation, but the report had not yet been received.

DISCUSSION

DR. WHITEHOUSE said he had not observed the patient as long as had Dr. Trimble, so it was not quite fair to criticize the diagnosis, but from what he had seen he rather favored the diagnosis of syphilis—from the scars that remained and the circinate group of papules. Of course the mere statement by the patient that it disappeared under medication would not influence him, but the appearance of the scars bore out what the patient said about their disappearing and recurring during a period of seven years, and all this was in favor of syphilis. He did not know that lupus disappeared and recurred, but syphilis could do so in one circumscribed locality like this.

DR. HIGHMAN said that Dr. Whitehouse had expressed his views.

DR. HOWARD FOX thought the diagnosis of syphilis more probable, as the patient presented a group of dull colored nodules arranged in a circle and situated largely on one side of the nose. He thought the age of the patient also favored this diagnosis.

DR. LANE said that if the history given by the patient was correct, the condition had existed for seven years; it would seem that if it were lupus there would be no question about the diagnosis by this time; accordingly, he favored the diagnosis of syphilis.

DR. POTTER also agreed with the diagnosis of syphilis.

DR. WINFIELD expressed the opinion that the fact that the condition was relieved by medication strengthened the diagnosis of syphilis. The patient had probably been taking potassium iodid, and such lesions sometimes yield readily under that treatment. The scarring and the circinate eruption all pointed strongly to syphilis.

DR. MACKEE said that he was surprised at the unanimity of opinion expressed about a duration of seven years being common for syphilis. It had not been his experience to see syphilis recur in a restricted area for over seven years. He agreed with the diagnosis of syphilis, but was surprised at the opinions expressed. He had never seen such a case.

DR. HIGHMAN, referring to Dr. MacKee's remarks, said that Jadassohn used to point out a circinate seborrheal type of nodular or papular syphiloderm that occurred in the nasolabial fold near the tip of the nose in late secondary or early tertiary syphilis. This case seemed to meet that description. It was peculiar to people with facial seborrhea.

DR. TRIMBLE said that he had seen the case only once several days before, and at the time there was some discussion in regard to these two diagnoses, so it seemed an interesting case for presentation. He had not heard the result of the Wassermann report. The only thing that surprised him was the

unanimous opinion that the condition was syphilis. He had expected that some would consider it lupus. At first glance the lesions strongly resembled those of syphilis, though after the history had been taken, and after thinking it over carefully, it seemed to him that it was a group of lupus papules. Some one had referred to the age of the patient. It seemed that all the members were taking the woman's history into too great consideration, where as a general rule little importance was given to the history of the case. The woman did say that the lesions disappeared entirely on one or two occasions after taking some internal medication. Patients, however, often say that when the lesion does not disappear entirely, but only improves. Nor should the age of the patient be given too much consideration. He thought we must change our opinion about its always beginning in the young. Cases are seen following the tuberculosis ulcerations that occur at the mucocutaneous outlets of the body; this condition after it encroaches on the glabrous skin at times changes into lupus vulgaris.

DR. TRIMBLE said that he would report the Wassermann reaction and the result of the therapeutic test at the next meeting.

DARIER-ROUSSY SARCOID. Presented by DR. WISE for DR. FORDYCE.

S. E., an Irish housewife, 35 years of age, presented two subcutaneous nodules just above the right knee, violaceous in color. The first, of one year's duration, was the size of a large walnut and situated anteriorly. The second, which was said to be of only a week's duration, was pea-sized and located laterally. There was no tenderness. Treatment with Fowler's solution had just been started.

DISCUSSION

A number of the members expressed their agreement with the diagnosis.

DR. HIGHMAN said that he agreed with the diagnosis clinically, and had also seen a slide which confirmed it.

ARSENICAL KERATOSIS AND PIGMENTATION. Presented by DR. WISE for DR. FORDYCE.

I. W., a Russian girl, aged 20, had had chorea for twelve years, and had been taking arsenic off and on during that time. She presented extensive arsenical keratosis of the palms and soles, with pigmentation; also mottled brownish discoloration about the neck. These effects were said to be of three years' duration.

FOR DIAGNOSIS. Presented by DR. TRIMBLE for DR. ROTHWELL.

An Italian, 45 years of age, presented plaques of nodular infiltration covering most of the dorsum of one hand, including backs of phalanges (proximal) and small areas over the thenar eminence of the other palm, the color of the infiltration on the dorsum of one hand being darker than his normal pigment. On the abdomen and thighs were scattered from ten to twenty brownish-red nodules of various outlines, some giving the impression of rings, the borders being thicker than the centers. On the dorsa of the feet were purplish pigmentations, well defined at the border, and without apparent infiltration.

History was of about one year's duration, and except for itching of areas of pigmentation on the feet there were no subjective symptoms. He was the father of five healthy children; his wife had had no miscarriages. He denied

any knowledge of having had syphilis, and his Wassermann reaction was negative. A biopsy was made, but the report had not yet been received.

DISCUSSION

DR. TRIMBLE said that the man was one of Dr. Rothwell's private patients, and he was very undecided about the diagnosis, and had brought him to the clinic for a biopsy. The two conditions considered were Kaposi's hemorrhagic sarcoma and lepra. The biopsy report had not yet been received, but it seemed to be an unusual case. The lesions on the body and those on the face and hands seemed quite different. The condition on the feet and hands resembled Kaposi's hemorrhagic sarcoma, though there were no nodules. He was inclined to consider it a case of Kaposi's sarcoma.

DR. HIGHMAN said that it was difficult to size up such a case at a glance without a detailed study, but the major clinical features undoubtedly suggested Kaposi's sarcoma.

DRS. MACKEE, HOWARD FOX and WISE agreed with DR. HIGHMAN.

DR. WHITEHOUSE also agreed with Dr. Highman that the case clinically suggested Kaposi's sarcoma. He then inquired about the lesions on the feet and hands, and said that he had thought the history was a little longer than stated by the preceding speaker. The infiltration and the pigmentation certainly suggested Kaposi's sarcoma.

DR. TRIMBLE agreed with the diagnosis of Kaposi's sarcoma, and said that he considered it Kaposi's sarcoma when he first saw the case. This diagnosis was based on the bluish areas of the hands and feet; the lesions on the body did not seem to resemble those of Kaposi's sarcoma. He promised to report the pathology of the case at the next meeting.

DR. WINFIELD said that he had had a case of Kaposi's sarcoma under observation for many years, and at times the patient had these blue discolored spots on the body, which sometimes disappeared without treatment. He expressed the opinion that these lesions would not argue against the diagnosis of Kaposi's sarcoma.

LICHENOID PAPULAR SYPHILODERM. Presented by DR. WISE for DR. FORDYCE.

G. B., a clerk, aged 29 years, had come under observation two days previously, when a blood test was made, the report of which had not yet been received. He stated that the previous Wassermann test was positive. When first seen the patient exhibited a rash having the appearance of lichen planus, pea-sized isolated flat papules being scattered diffusely over the trunk and the inner surface of the thighs. On presentation, however, the resemblance to lichen planus was remote. The man gave a history of being married and of having had no extramarital intercourse, and no sign of any chancre on any part of the body; but stated that a maid in the house had been taken to the hospital on a stretcher with a generalized rash, the nature of which he did not know.

Diagnosis accepted without question.

UNILATERAL VASCULAR NEVUS. Presented by DR. HOWARD FOX.

V. S., a school boy, 14 years of age, born in the United States, presented an extensive "port wine" nevus of the upper and lower extremities of the

right side. The patches varied in size and shape, being darkest on the most dependent parts. On the lower extremity they extended from the sole to within a short distance of the anterior superior spine. On the upper extremity they were present on the palm, the back of the hand and the forearm. His hand was being treated by the Kromayer lamp (with pressure).

SYPHILIS OR LICHEN PLANUS? Presented by DR. HOWARD FOX.

A man, 30 years of age, referred by the U. S. Public Health Service, had been infected with syphilis two years previously while in the military service. His Wassermann reaction was said to have been positive at the time of infection. He had been treated by seven injections of arsphenamin and forty intramuscular injections of mercury, and his Wassermann reaction had been twice negative during the past year. Four weeks ago he noticed for the first time an eruption on the glans penis. This consisted of a half dozen pinhead sized, flat, dull colored papules, several of them presenting a central depression. There was no itching or other subjective symptom. He had not recently received any antisyphilitic or other treatment. He was presented for differential diagnosis between localized lichen planus and late secondary syphilis.

DISCUSSION

DR. MACKEE said that one could not differentiate clinically between the two conditions, but would have to depend on the therapeutic test and the Wassermann reaction.

TABES DORSALIS WITH CHARCOT JOINT (?). Presented by DR. HOWARD FOX.

A man, 54 years of age, referred by the U. S. Public Health Service, had suffered from a penile lesion twenty-seven years ago, though he gave no history of secondary manifestations. He had been treated with pills for about two months. The lesions of the toes were first noticed fourteen years ago, beginning as "corns" followed by ulceration of the great and second toes of the right foot. The left great toe had been amputated five years ago. During the past four months he had suffered from a swelling of the left knee joint, which was at times painful, though not tender to the touch. This had appeared without any preceding traumatism. He gave a history of bladder disturbance, lightning pains and loss of sexual power. He presented an Argyll Robertson pupil, Romberg symptoms and absence of knee jerks. Radiograms made by Dr. Foster showed: "Loss of the outer distal portion of the terminal phalanx of the left foot. Right foot shows loss of phalanges and distal half of metatarsal bone of great toe and phalanges of second toe and metatarsal bone of small toe. Lower end of femur shows erosion of outer condyle of lower end of femur." The blood Wassermann test was +. Examination of the spinal fluid (made at the Marine Hospital) showed normal findings, the cell count being 6 and the Wassermann reaction, globulin and gold curve being negative.

There were no macules suggestive of maculoanesthetic leprosy to be seen on any part of the body. The ulnar nerves appeared to be slightly enlarged, though not tender.

The patient appeared to be in good general health, with fairly strong muscles, and was well nourished. A neurologic examination by Dr. Charles A. McKendree was made subsequent to the presentation of the patient. His report was:

"Considerable swelling and deformity of the left knee. Great toes of each foot removed. Cyanosis of both feet. No special atrophy. Sphincter control is disturbed. Sexual power absent twelve years. Marked Rombergism. No ataxia of the upper extremities. No dysadiadokokinesis. The vibratory senses in the legs and arms are preserved. Position sense is markedly disturbed in the toes. Touch is preserved all over the body, except for diminished sensation on the outer side of the left leg and over the dorsum of the foot. Pin prick corresponds; warm and cool stimuli correctly interpreted, except for possibly some delay, but specially affected on the outer surface of the left leg. Reflexes of the upper extremities are present and equal. Patellar and Achilles' jerks are absent on both sides. Pupils are about equal. The left is slightly irregular; convergence reaction present; light reaction absent. Right fundus shows several extensive scars, the disk is not well made out. The left fundus shows a small scar over the disk. The disk appears fairly normal.

"Diagnosis: Neurosyphilis of tabetic type. Charcot joint."

DISCUSSION

Dr. Foster showed a plate made in the afternoon, and expressed his regret that he had not been able to find one taken three years ago. There had been some changes in the phalanges since the patient was last seen. In the left foot there was destruction of the two terminal phalanges and part of the proximal phalanx of the great toe. The knee showed some erosion of the condyles, but there was nothing characteristic of sarcoma, which was the tentative diagnosis when under observation at the dispensary. The laboratory examination was all against the diagnosis of syphilis; the blood Wassermann reaction was +. The patient was born in Austria, near Trieste, but had visited all parts of the world and had had relations with women in every country where he had wandered practically all his life. He gave a history of venereal ulcer twenty-seven years ago, but no history of secondary infections.

Dr. Whitehouse said that the patient presented more symptoms of leprosy than of any other condition. Two out of five cases of lepra give a + Wassermann reaction. Dr. Whitehouse said he did not think the changes shown conformed to syphilis and was inclined to consider it a case of leprosy. He had seen patients, one from the West Indies, with both syphilis and leprosy—deforming leprosy of the hands, toes and fingers, and blindness, together with active lesions of syphilis. They had the changes of leprosy and frank syphilis at the same time.

Dr. Highman said that the patient stated he was born in Istria and had gone to Melita, where a disease prevailed which is related to syringomyelia or is identical with it. The + Wassermann reaction might go with either syphilis or lepra, but was too weak to be significant. Nevertheless, the patient had Romberg's sign, Argyll Robertson pupils, Charcot's knee, etc. There was also clinical evidence of pressure on the roots. The + Wassermann reaction could be taken for what it was worth, but in neural leprosy the Wassermann reaction was usually negative. There was nothing abnormal about the ulnar nerve of this man, so the evidence favored syphilis rather than leprosy. On the other hand, the mutilation of the toes was against syphilis and somewhat favored leprosy, but not more so than syringomyelia; though whether that condition was accompanied by the disturbances which the man showed, he could not recall. On the whole, he was more inclined to the diagnosis of syringomyelia than any other condition.

Dr. Lane thought that a positive diagnosis in this case could not be made on the basis of the data presented. The bone changes and the deformities of the feet could easily be attributed to leprosy, and it was possible that the changes in the bones of the knee joint also might be attributed to it. The Romberg symptom, which was slight, might be accounted for by the condition of the knee joint without the necessity of explaining it by involvement of the central nervous symptom. It was possible that both syphilis and leprosy were present. Further examination should settle this question, and should also determine whether the condition was leprosy or syringomyelia.

Dr. Potter favored the diagnosis of leprosy rather than syphilis.

Dr. George H. Fox expressed his regret that he had not been able to make a careful examination of the case, but doubted that it was leprosy. In leprosy there may be ulceration and loss of the phalanges, but he did not know that it ever produced the osseous atrophy seen in this case. He was inclined to agree with Dr. Highman's suggestion that it was some other disease than either leprosy or syphilis.

Dr. Wise said that Dr. Highman's suggestion had appealed to him also. If the man had enough leprosy to develop the deformity of the feet as shown, he would also show other conditions which would be recognized at a glance. It would be well to study the case along the line of Dr. Highmann's suggestion.

Dr. Winfield was inclined to agree with Dr. Highman's diagnosis. He had seen some cases of Morvan's disease in which there were the same changes in the osseous tissues. The lightning pains did go with Morvan's disease—also with leprosy and with syphilis. In his opinion the diagnosis of Morvan's disease was more likely than either syphilis or leprosy.

Dr. Howard Fox regretted that he had only the opportunity of making one brief examination of the patient. He did not think the case one of leprosy. With such marked changes in the toes in leprosy we would expect to find other changes, such as anesthesia, pigmentation, enlarged ulnar nerves, etc. The diagnosis of anesthetic leprosy might be settled by microscopic examination of the nasal mucous membrane. As the patient presented an Argyll Robertson pupil, loss of knee jerks, a possible Charcot's joint, and complaint of lightning pains and bladder disturbances, a probable diagnosis of tabes had been made. The changes in the toes, however, did not seem to accord with this diagnosis, which he thought was also weakened by the negative Wassermann findings in the spinal fluid. The idea of Morvan's disease had not occurred to the presenter.

Dr. Foster said that three years ago, when he first saw the patient, he had thought of leprosy and syphilis, but the changes in the bones of the feet, as shown by the roentgen ray, pointed against syphilis; there was no bone production, and with a + Wassermann reaction, a negative spinal fluid, and a cell count of 6, it did not seem to be syphilis. The man was a sailor, and had been exposed to both diseases in his travels all over the world.

Dr. Foster said that he had entirely overlooked the possibility of Morvan's disease, and it had never occurred to him until suggested by Dr. Highman. In his mind it had been a question of diagnosis between syphilis and leprosy, and he had submitted the case for an opinion on the matter.

CASES PREVIOUSLY PRESENTED.

Dr. Highman said he wished to report on the case of lichen hypertrophicus. Histologically the diagnosis was confirmed. After a roentgen-ray examina-

tion a marked involution of the lesions took place, and he hoped to be able to report more later.

DR. WINFIELD said that he had recently seen an interesting case of syphilis and Vincent's angina occurring simultaneously. The patient was taken ill six weeks ago with temperature and sore throat and a membrane. The attending physician diagnosed the case as diphtheria and sent a culture to the board of health. The report came back negative. A culture was also sent to a private laboratory, and they reported Vincent's angina. The throat symptom cleared up under treatment, but the man did not get well; so he was examined further and a ++++ Wassermann reaction was obtained. He then said that during the summer he had a pimple on the shaft of the penis. No eruption followed, and his throat is now practically well.

DR. HIGHMAN said that in the army he saw several cases of so-called Vincent's angina, and discussing the matter with laboratory workers, he got the impression that the organisms of that disease were not of established pathogenicity. In one instance a gumma of the tongue showed the organism of Vincent's angina; the patient was treated with arsphenamin and the lesion healed. But a buccal gumma might show these organisms if they were saprophytes, and the lesions might heal with intravenous therapy. In another case there was a negative Wassermann reaction, and the local application of arsphenamin used as a dusting powder worked well. What the real truth of the pathogenesis of Vincent's angina is, he did not know.

NEW YORK ACADEMY OF MEDICINE, SECTION ON DERMATOLOGY AND SYPHILIS

Regular Meeting, Nov. 3, 1920

JOHN E. LANE, M.D., *Chairman*

EXTENSIVE VERRUCAE OF FEET. Presented by DR. TRIMBLE.

T. L., aged 36, a Porto Rican, had a negative family history. His personal history was negative. Present Condition: The lesions began on the dorsum of the left foot twenty-five years ago as small warts. The patient at that time was working barefooted in the tobacco and sugar fields of Porto Rico. The lesions gradually increased in size, and at the end of six months spread to the dorsum of the right foot. The lesions have continued to enlarge and spread until they have attained their present size. A few years ago after scratching the feet and getting blood on the fingers, the patient noticed lesions on the fingers. The eruption consisted of discrete and confluent brownish, verrucous lesions, varying in size from that of a small pea to that of a pigeon's egg, covering the feet and extending up the leg; they were also on the fingers.

Laboratory Report: The Wassermann reaction was negative. Pathologic Report: Verruca.

CUTIS VERTICIS GYRATA. Presented by DR. TRIMBLE.

A young man, aged 25, had noticed for four years some slight ridges in the anterior part of his scalp, which seemed to be deepening as the years went by. The condition at present consisted of a number of rather deep sulci

with corresponding ridges running longitudinally along the front of the scalp. The lesion apparently started about one-third the distance back from the forehead, and seemed to become more prominent as they ran forward. The patient had a good growth of hair, though it was lost in some areas in front.

DISCUSSION

DR. LEVIN said that the case which he and Dr. Wise reported showed transverse ridges and furrows over the occipital region of the scalp, and he recollected that there were distinct signs of a pituitary type of person. The cause of the condition in their case could not be determined. This condition also occurred in a patient with pituitary markings, and it is possible that further study may disclose a relation between endocrine disorder and the structural changes in the scalp.

MULTIPLE HEMORRHAGIC SARCOMA OF KAPOSI. Presented by DR. TRIMBLE.

A man, aged 62, a Jew, whose family and personal history were negative, presented a condition which began six years ago on the left foot. The condition appeared as blotchy diffuse redness; two years later the redness appeared on the right foot; two and one-half years after this small tumors appeared on both feet and legs, with no accompanying symptoms, except slight edema. The tumors had not increased in size; the lesions were limited to the lower part of the legs below the knees. Both feet presented purplish brown discolorations with many tumors scattered over them, ranging in size from that of a small pea to that of a bean. The laboratory reported the Wassermann test negative. Pathologic Report: Multiple hemorrhagic sarcoma.

LICHEN RUBER ACUMINATUS. Presented by DR. TRIMBLE.

A man, aged 37, a German, whose personal history was negative, six years ago developed pruritus of the feet, which gradually spread up the legs. No eruption was noticed at this time. The patient was accustomed to rubbing the entire body with alcohol each day. January, 1920, the present trouble began. The eruption began as scaling and pruritus of the scalp. In one week the eruption spread downward, involving the entire body; it was nonpruritic except when the body was dry. The eruption consisted of reddish discrete papules; over the greater part of the body they were confluent. The papules were follicular and scaly; the palms and soles greatly thickened. The Wassermann reaction was negative.

LICHEN PLANUS (?) IN A SYPHILITIC PATIENT. Presented by DR. WISE.

N. P., aged 28 years, single, a painter, French, had been receiving antisyphilitic treatment at the Vanderbilt Clinic since March, 1920. The lesions in question were situated on the prepuce and glans penis and on the inner aspect of the left leg. They first appeared on the penis in January, 1920, and on the leg a month ago. On the penis were several discrete and confluent purplish papules. The lesion on the leg was the size of a quarter, of violaceous hue, and covered with fine adherent scales.

EPIDERMOLYSIS BULLOSA. Presented by DR. ROTHWELL. (From the service of Dr. Trimble.)

An Italian boy, 5 years old, presented a generalized eruption of ruptured and crusted, as well as unruptured bullae, the legs, arms and face presenting most involvement, though the trunk presented a few ruptured lesions. There was little of areola about the lesions, some being as large as a half dollar, others not larger than a ten-cent piece.

The parents stated that the condition had been present since birth, but the lesions last only a few days. Bullae could be produced by scarifying the skin and by twisting it between the fingers.

NEVO-HEMANGIO-LYMPHANGIOMA OF THE LEFT LEG. Presented by DR. ABRAMOWITZ.

Richard O'C., 15 years old, born in the United States, had had skin disease since birth. He presented himself at Dr. Fordyce's clinic, stating that for the past five years his left leg had been getting thicker. Beginning on the dorsum of the left foot were large, livid, flat patches which extended almost continuously up to the middle of the thigh. Some of these patches were covered with verrucous lymph vesicles (lymphangioma), and other patches were made up of soft cavernous angiomas. Varicose veins were also present on other parts of the leg.

ACRODERMATITIS CHRONICA ATROPHICANS. Presented by DR. ROSTENBERG.

A woman 52 years old, born in Russia, married thirty years, had never been pregnant. Her family history was irrelevant. She had always been well, but had always been easily chilled. Her present skin trouble began about four years ago with pain and swelling of the legs. She was a fairly well nourished woman. The internal organs were normal. The urine was normal and the Wassermann reaction was negative.

The skin lesion extended over both limbs and buttocks, sharply ending at the iliac crests. Anetoderma was well marked at both knees and buttocks. The skin over both tibiae and feet appeared bluish red, transparent and thinned out, the subcutaneous veins appearing most prominently in these areas. The hands and forearms were not involved.

ACRODERMATITIS CHRONICA ATROPHICANS. Presented by DR. ROSTENBERG.

Mrs. R. H., aged 40, born in Austria and for seven years resident in this country, was never sick, except for a severe burn which she sustained eighteen years ago over the same area which was involved on presentation. Her present skin trouble began, however, only three years ago, with pain and swelling of both feet, soon involving the entire legs. The legs and buttocks were involved, leaving free a sharply defined triangular area on the outer aspects of both legs. The skin over the knees showed the characteristic pigmented infiltration and marked anetoderma. The same condition was present on the buttocks. The skin over the tibiae, and especially over the dorsum of both feet, was very much atrophied and transparent, the underlying veins showing plainly. There was a small ulceration over the right outer malleolus, and another larger one over the tibial region. The hands and forearms were not involved.

NODULAR LEPROSY. Presented by DR. ROTHWELL. (From the service of Dr. Trimble.)

An Italian woman, married, 29 years of age, presented a typical leonine countenance, with some loss of eyebrow; there was a nodule on the sclerotic coat of the left eye; she had much thickened ulnar nerves; there were various areas of anesthesia on trunk. The duration of the condition was two years. She had been eighteen years in the United States.

Biopsy demonstrated the presence of Hansen's bacilli. The Wassermann reaction was ++++. An apparent improvement was noted after a course of six intravenous arsphenamin injections.

NEVUS UNIUS LATERALIS. Presented by DR. ROTHWELL. (From the service of Dr. Trimble.)

An Italian girl, 14 years old, presented a hypertrophied, pigmented mole on the left cheek, involving the vermilion border of both lips and mucous membrane lining both lips. The cutaneous lesion on the cheek was irregular in outline, the hypertrophy being loose and pendant, and gradually narrowing to a line about one-eighth inch broad as the angle of the mouth is approached. The portion involving the vermilion border was verrucous in character.

DERMATITIS HERPETIFORMIS. Presented by DR. ROSTENBERG.

The patient, 17 years old, born in New York, came of healthy parents, and was one of eight children, of which five died in infancy. The patient claims that her present illness followed an attack of chickenpox when she was 5 years old, and that she had never been free from it since. She came under observation at the Mount Sinai Hospital in Dr. Rosen's service about three years ago, at the age of 14. With the exception of her skin trouble, she appeared to be in good health, and gave the impression physically as well as mentally of a much older woman. Menstruation began at the age of 9, and she claimed to have been fully developed at that time.

She presented a large number of areas all over her body, which resembled an acute weeping eczema, and a tentative diagnosis of infectious dermatitis was made. Endocrine disturbance was suspected, and she was given thyroid in addition to ointment. The improvement was slight and not lasting; one attack would follow the other, and on account of the grouping of the lesions and the extreme itching, the diagnosis of dermatitis herpetiformis was made. A roentgen-ray picture of her head revealed a small sella turcica with bridging of the clinoid processes. Pituitary extract had as little effect as thyroid extract.

DISCUSSION

DR. ABRAMOWITZ said that the eruption had the appearances of a neurodermite. The history obtained was that the itching occurred first, followed by the appearance of papules.

DR. HIGHMAN said that he had observed the patient for a year, off and on, and that she had a dermatitis herpetiformis, although she did not show it when presented.

DR. ROSTENBERG said that the diagnosis of the condition as presented was difficult, but when the patient first came under his observation the question of infectious dermatitis came up, and finally this grouping of dermatitis herpetiformis was observed and the diagnosis was made. The condition had cleared

up and the patient was better than she had ever been, but every once in a while she has a terrific attack of dermatitis herpetiformis.

DERMATITIS EXFOLIATIVA FOLLOWING PSORIASIS. Presented by DR. TRIMBLE.

The patient was a Jewish woman, aged 31, whose family and personal history were negative. The present illness began at the age of 14. The lesions started on the elbows and knees, finally spreading over the entire surface of the body. The eruption had cleared up several times under treatment, but it returns in from a few months to about two years. The eruption was confluent, generalized, red and scaly. There was extreme scaling in the hair.

SKIN LESIONS ASSOCIATED WITH EVIDENCES OF ENDOCRINE DISORDER. Presented by DR. LEVIN.

Patient was presented at the March, 1920, meeting of the section.

Abstract of History.—Y. Z., a married woman, aged 38, a Russian, had had measles and typhoid in childhood. She had a pelvic operation thirteen years ago and tinea saginata one year ago. Menses began at 13 and were irregular and scanty. There was no dysmenorrhea. She had been married sixteen years; she had had five children; two were dead from accidents.

The skin condition was of seven years' duration. It began with pruritus, and after two years distinct hyperhidrosis was noticed. For two years the pruritus had been intense; the sweating had increased markedly; attacks of erythema with excessive sweating appeared now and then. A generalized increased pigmentation and oozing eczema had developed.

General symptoms had been present for two years. There were loss of weight and strength and she tired easily. She had almost constant headache (frontal); a capricious appetite, constipation, urination hourly and loss of sexual desire.

Skin Condition in March, 1919.—The skin was dry, thickened, pigmented, roughened, and covered with follicular papules. There was generalized lichenified and vesicular eczema which was most distinct on the face, neck, upper extremities and waist line. The hair was black, dry, coarse, and thinned, especially in the axillae and pubic region. Her hands were cold and moist.

Endocrine Markings.—She had had measles and typhoid in childhood. She had dry, thickened skin, dry hair, attacks of erythema and sweating, alopecia and constipation; the basal metabolism was lessened.

She was of a pituitary-skeletal-small stature with small bones, stubbed fingers, small chin, small, separated teeth, increased glucose tolerance and polyuria.

Suprarenal-increased pigmentation, low blood pressure, scoliosis with flat feet, loss of strength, increased fatigability, pigmented tumor (chin); gonad-loss of sexual desire, scanty menstrual flow, sweating and flushing were also present.

Diagnosis: Skin lesions associated with pluriglandular disorder.

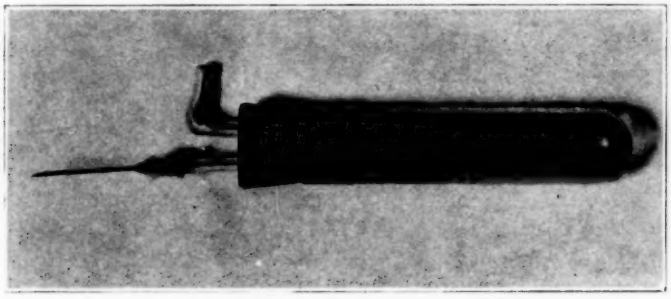
TINEA OF NAILS ON THE HANDS; KERATOSES (TINEA?) OF SOLES OF FEET. Presented by DR. WISE.

D. H., a Russian woman, aged 30 years and married, presented herself at Professor Fordyce's clinic, giving the history of trouble with her nails for one

year. The nails showed a fine stippling, some of which was arranged in transverse and longitudinal lines. The soles and heels showed keratotic brown patches, varying in size from that of a five-cent piece to that of a quarter, all of three months' duration. There were many deep rhagades in the keratotic patches, which occasionally bled.

DEMONSTRATION OF A SUBSTITUTE FOR THE McRAE NEEDLE. DR. LANE.

Dr. Lane said that the McRae needle was an excellent device for drawing blood in cases in which aspiration was necessary for getting the desired amount. The difficulty of cleaning the needle and the inconvenience of having needles of only one size available, had led him to devise a substitute which he had found quite satisfactory. This substitute consisted of a small glass tube, ground at one end to fit a Luer needle, put through a rubber stopper, together with another glass tube for attachment to the aspirating tube. In case a small necked centrifuge tube is used, the stopper is not large enough to take both



A substitute for the McRae needle.

glass tubes, and a needle of large bore is substituted for the glass aspirating tube and an ordinary adaptor is used to connect it with the rubber tubing. This apparatus is inexpensive, easy to clean and by varying the size of the needle and stopper it may be used on any bottle and any desired amount of blood may be easily withdrawn.

Dr. Lane also demonstrated an apparatus for the alkalinization of arsphenamin solutions, a detailed description of which will shortly appear in *The Journal of the American Medical Association.*

NEW YORK ACADEMY OF MEDICINE, SECTION ON DERMATOLOGY AND SYPHILIS

Regular Meeting, Dec. 7, 1920

JOHN E. LANE, M.D., *Chairman*

GRANULOMA ANNULARE, SHOWING THE EFFECT OF ROENTGEN-RAY THERAPY. Presented by DR. CHARGIN.

Mr. K. was presented before the section in 1915, with typical lesions of granuloma annulare on the backs of the hands, fingers and ears. From that time until 1919 he had been receiving roentgen-ray treatment, having received

a total of 12 skin units. He had received no treatment of the hands during the past year, and there had been no recurrence of lesions on the hands, although he had developed a mild degree of telangiectasia at the sites of exposure. He still exhibited some of the old lesions on the ears and neck and had developed new areas of granuloma annulare on neck and cheeks.

ACTIVE SECONDARY SYPHILIS (PUSTULAR SYPHILIDS). Presented by DR. LEVIN.

T. N., an Italian, aged 27, unmarried, a diver, stated that the eruption had been present for four weeks. He left Italy just before the appearance of the eruption. The chancre appeared about eight weeks before presentation. Sore throat, headaches and falling of the hair accompanied the eruption.

The skin showed a generalized, bilateral, follicular and nonfollicular papular and pustulopapular eruption. On the face, scalp and trunk there were also several pea-sized, scaly, ham-colored papules. There was a healing chancre on the prepuce. There was an extensive alopecia of the scalp, most marked in the frontal region. He also had a generalized adenopathy, mucous patches and pharyngitis. A Wassermann test had been made, but the report had not been received.

PARAPSORIASIS. Presented by DR. CHARGIN.

E. B., a man, single, 25 years of age, a painter, had an eruption which began about ten months ago. At that time the patient presented a faint macular eruption on the back and a mixture of papules and macules on the arms, buttocks and upper part of the legs. The eruption on the back had since involuted. When presented, the eruption was limited to the arms, buttocks and outer part of the legs, and was made up of a network of macules with scattered small papules. There was likewise a faint macular eruption on the back. The papules showed a scaling which was small and white. The general color of the eruption was pale red. There was no scarring or atrophy. Subjectively, there was no itching, but there was occasional burning. The Wassermann reaction was negative.

Dr. Chargin stated that when first seen the diagnosis in this case was somewhat puzzling. The eruption on the body strongly suggested a macular syphilid, although that on the arms and buttocks looked more like seborrheic eczema. The diagnosis of syphilis was, however, ruled out by the history and the subsequent course of events. Seborrheic eczema could be excluded by the lack of involvement of the scalp and face, and the character of the scales, which were of the seborrheic type. Moreover, the liberal use of a mixed chrysarobin ointment had no influence on the eruption.

URTICARIA PIGMENTOSA. Presented by DR. WISE.

L. F., aged 42, a painter, born in the United States, presented himself at Dr. Fordyce's clinic with an eruption on the back, buttocks and axillae, which had been present about two years without any intermission. The patient complained of moderate itching. As presented, the patient exhibited numerous split-pea sized papules of an erythematous shade, which, as they faded, left a brown pigmented macule.

DISCUSSION

DR. HIGHMAN said that he had seen a section of the tissue, but on account of the difficulty in staining it he was not sure whether there were cells. The

infiltration corresponded to xanthelasmoidea, and involution was taking place in the way described by Hartzell. He said that often in this disease the mast cells could no longer be recognized during involution. Nevertheless, the general structure of the tissue indicated urticaria pigmentosa, which, considering the age of the patient when the condition began, brings up the point whether there is a form that can be called urticaria pigmentosa acquisita.

Dr. Abramowitz said that the question brought up by Dr. Highman was interesting. Quinquad mentioned a number of cases acquired by adults. There had been a few patients at the Vanderbilt Clinic in which clinically the eruption seemed to be xanthelasmoidea, yet the mast cells could not be found in the section. The French called these cases maladie pigmentie urticant.

Dr. Fraser said that we should be on our guard against calling these cases urticaria pigmentosa unless the mast cells were found in the section. As he understood it, urticaria pigmentosa was rather rare in adults. The last case that he saw so diagnosed in an adult proved to be scabies, and the patient became well under treatment for scabies.

Dr. Highman said he was willing to guarantee from the clinical appearance that this was not a case of scabies. As a matter of fact, urticaria pigmentosa disappears at about the age of adolescence, the lesions leaving small brownish lentiginous spots. Unquestionably there were no mast cells in these spots. Somewhere during involution the mast cells must vanish, and for that reason Hartzell's contention seemed probable. Urticaria pigmentosa can exist as a recognizable clinical picture, yet a given lesion may not show the pathognomonic structure.

In regard to an inquiry by Dr. Lane relating to the precise clinical difference, Dr. Highman said that it was similar to that of prurigo, without many mast cells and ordinarily the finding of chronic inflammation.

Dr. Oulmann said that this patient did not complain of itching at any time during the outbreak; while therefore scabies must be entirely excluded, the diagnosis of urticaria pigmentosa is doubtful. A number of years ago, Dr. Oulmann presented a case which afterward was also presented by Dr. Bechet; the condition had spread and the patient had lesions in the mouth. Dr. Oulmann's diagnosis was xanthoma planum et elevatum, and the condition consisted of similar brownish, slightly elevated and flat tumors. The present case was not so far advanced. The only difference was that in Dr. Oulmann's case there were lesions also over the sacral region, a place of predilection. The microscopic picture does not indicate urticaria pigmentosa. The case has to be followed up further.

Dr. Pollitzer said he wished to call attention to a fact that seemed to have escaped some of the members, i. e., that this man presented urticarial wheals, not only fixed papules, but wheals that appeared on irritation.

Dr. Lane asked whether there were any without irritation. That was the point.

Dr. Wise said he was not certain about the last point, but thought the patient had wheals only when the skin was scratched or irritated. The speaker believed, with other observers, that a form of urticaria pigmentosa in adults occurred in which mast cells were not always demonstrable.

PEMPHIGUS VULGARIS. Presented by Dr. Scheer.

A. W., a man, aged 44 years, a subway guard, was a patient in Dr. Fordyce's clinic. The condition began three months before presentation with sore throat

and hoarseness. The hoarseness disappeared in three weeks, but he complained of sore throat. The patient presented several erosions in the mouth, the sites of ruptured vesicles; the largest of these was on the right tonsil. Irregularly scattered over the chest, back and abdomen were crusted lesions varying in size from one-eighth to three-fourths inch in diameter. These had all begun as vesicles or bullae. There were also some light-brownish pigmented spots where the crusts had fallen off. The patient was apparently in good health. He had lost 2 pounds since the onset of his illness.

MALUM PERFORANS PEDIS AND ALOPECIA OF THE THYROGONADAL TYPE IN A SYPHILITIC PATIENT SHOWING DEFORMITIES OF THE SELLA TURCICA. Presented by DR. LEVIN.

J. S., a married Italian, aged 41, a laborer, applied for treatment of a painful ulcer of the left foot two months ago. The family history and past history were negative for syphilis. The ulcer of the left foot appeared about two years ago and has always been painful.

The left foot showed two deep ulcers on the plantar surface. The larger was situated over the first metatarsophalangeal joint. It measured about half an inch in diameter, was round, deep, surrounded by a horny growth, and led to a sinus discharging a seropurulent fluid. The second ulcer on the third metatarsophalangeal joint was smaller and not so deep. The plantar surface of the right foot showed hyperkeratotic patches over the metatarsophalangeal joints with beginning ulcers. The skin of both legs in front and in the region of the knees showed large, pigmented, cigaret-paper-like scars. There were hyperhidrosis and bromidrosis of the feet.

The skin of the rest of the body was white, soft and of fine texture and resembled that of a female. The hair of the eyebrows and eyelashes was missing. The mustache region and beard showed patches of baldness, and the rest of the hair was thinned out. Both axillae showed a sparse growth, and the pubic hair was of the female type. The forehead was wide; the frontal bosses, the glabella and the superciliary ridges were prominent. There was a marked separation of the incisor teeth. The pelvis was of the female type, and the voice also was feminine in character. The Wassermann reaction of the blood was +.

A radiogram of the skull showed a small, shallow, deformed sella turcica, and the anterior clinoid process was enlarged and deformed.

DISCUSSION

DR. LEVIN stated that he had presented the case to show the peculiar alopecia present in the patient, rather than the perforating ulcers. The patient had syphilis and showed the markings of a pituitary type of person. He showed an absence of the eyebrows and eyelashes. There was alopecia of the beard and mustache; the axillary hairs were very much thinned out, and the pubic hair was of the female type.

According to Leopold-Levi, the growth of the eyebrows and eyelashes is controlled by the thyroid gland; the growth of the axillary hairs and the pubic hairs is controlled directly by the gonads, and the pituitary gland acts only indirectly through the gonads on the growth of hair. This person therefore is a pituitary type with thyrogonadal alopecia, according to the findings of Leopold-Levi.

Dr. LeWald said that he would like to see the roentgenogram. Recently he had spent an afternoon in a Boston clinic studying pituitary fossa variations, and they were quite at sea there in regard to the normal pituitary fossa; there are so many variations in the supposedly normal person that one has to be very cautious in expressing an opinion as to the function of the pituitary gland from an inference of the so-called abnormal form of the pituitary fossa or over-riding clinoid processes. One would find extreme variations in 100 persons. Dr. E. W. Caldwell examined the frontal sinuses of 100 persons; he found such extreme variations that unless there is great erosion or great enlargement, such as is seen at times, one must be very cautious in drawing a conclusion from a mere prominence of the clinoid processes and apparent smallness of the fossa.

Dr. Levin said the report on the radiographic findings in this case was that obtained from the roentgen-ray department of the Cornell University Medical College and Clinic. Those of us who do not specialize in this branch of medicine must accept the reports of the experienced worker. Of course, we recognize the fact that it is yet impossible to state positively what constitutes a normal sella turcica as seen with the roentgen ray.

ORIENTAL SORE. Presented by Dr. Chargin.

C. L., a man, aged 19, single, a tailor, a native of Turkey, who had been in the United States about four months, had a lesion of eight months' duration, which began as a small sore that gradually increased in size until it became as large as a five-cent piece. During the last two months it had been undergoing involution. The lesion was located on the lower lip at the left corner of the mouth, on the vermilion surface, and was the size of a ten-cent piece when presented. It was somewhat hard and covered with a crust, the removal of which disclosed an irregular ulcerated base. There was a moderate amount of submaxillary adenitis. Smears for spirochetes and for Leishman bodies were negative. The Wassermann reaction was negative. The patient had received three intravenous arsphenamin injections.

DISCUSSION

Dr. Chargin stated that the first impression gained was that the lesion was a chancre, but this theory had to be discarded when numerous examinations for spirochetes proved negative. Moreover, there was absence of a marked submaxillary adenitis; the Wassermann reaction was negative; and there was absence of either a history or evidence of a secondary eruption. Gumma was ruled out by the absence of syphilitic history, a negative Wassermann reaction, consistency of the tumor, the presence of adenitis, and lastly by the course of the condition. Epithelioma was likewise considered. This diagnosis was improbable on account of the youth of the patient; also the glandular enlargement was not sufficient in amount; and that which was most important was the fact that the lesion showed definite involution which seemed to exclude epithelioma. With the knowledge that he recently arrived from the Orient, oriental sore came to mind, and although we have thus far not been able to demonstrate the Leishman bodies, the diagnosis of oriental sore seems justified both by exclusion and from clinical findings.

Dr. MacKee said he could not question the diagnosis because he had never seen an oriental sore; he hoped this would prove to be a case so that we could profit by the experience. He had, however, been wondering whether the pos-

sibility of tuberculosis had been considered. Clinically the lesion was of the character that suggested that possibility, although the enlargement of the glands of the neck did not occur so often in tuberculosis.

Dr. Highman said that his knowledge of the oriental sore was about equal to what he knew of the ductless glands, only he would like to caution Dr. Chargin against ruling out epithelioma on account of the youth of the patient. That was rather dangerous, as he had seen epithelioma in a girl of 17.

Dr. Pollitzer said he had been impressed with the word ulceration in Dr. Chargin's presentation. Was the lesion an ulcer when he first saw it?

Dr. Chargin, replying to Dr. Pollitzer, said that the lesion was covered with a crust, the removal of which revealed an irregular ulcerating sore.

Dr. Pollitzer said that the evidence was in favor of the diagnosis submitted, though it was based chiefly on exclusion. It was an easy matter to rule out the various possibilities mentioned; but the fact that the lesion resembled an involuting Aleppo boil, and that the man came from the Aleppo boil region, together with the negative evidence, seemed to be sufficient reason for accepting that diagnosis as probable.

Dr. Williams said it was a very interesting case. At first sight it suggested the primary lesion of syphilis, but on careful examination that could be ruled out. It was impossible to exclude Aleppo boil, and that was the probable diagnosis. The boy, however, had the habit of licking the side of the mouth and keeping it constantly wet with saliva, and it was possible that it was an ordinary granuloma kept irritated by constant licking and wetting.

Dr. Howard Fox said that he had recently had the opportunity of studying a case of oriental sore at Ellis Island. In this case the lesions were all situated on the face, following the general rule of being present on the exposed parts. While most authorities stated that the eruption generally consisted of a single or at least few elements, in his case there were ten distinct lesions. The diagnosis had been confirmed by finding the Leishman-Donovan bodies in the sections. According to the experience of others, the clinical diagnosis was often difficult. Castellani and Chalmers stated that there were six distinct clinical types. In some cases the differential diagnosis between syphilis, tuberculosis and blastomycosis was difficult, and could only be definitely settled by finding the organism in smears or sections.

Dr. Satenstein said that he had had opportunity to study sixty-two or sixty-three cases, some from Damascus, some from Aleppo and some from Turkey. Two types were found—one from Turkey, and the other (the breaking down type) from Damascus and Aleppo. The lesions always appeared on the exposed parts of the body. In all the cases he saw only two had single lesions, one of them on the nose of a boy of 5, and the other on the cheek of the patient. All the other cases were multiple, one of them having eighty or ninety lesions. A Wassermann test was made before, during and after treatment. Practically every case responded to arsphenamin, but not to arsphenamin as given here—once a week—but three times a week together with local treatment. Some of the eruptions involuted as a result of ordinary cleanliness without treatment. In from four to six weeks the lesions disappear, and they appear only on the exposed parts. Dr. Chargin mentioned that his patient was receiving arsphenamin. The lesion had the pearly border and the softness that corresponded to many of the cases seen. As for the microscopic examination, Dr. Satenstein said they had never accepted a case of oriental sore unless the organisms were found. They always made an incision at the

margin of the lesion, curetted some of the tissue, and looked for the living organisms. He could not recall that a successful smear had been made at any time. The organism was found in the tissues and in the fresh preparations, but never in a stained smear.

DR. HIGHMAN inquired how rapidly the cases responded to arsphenamin.

DR. SATENSTEIN replied that six weeks was the shortest time required.

DR. CHARGIN said that the textbook descriptions usually state that the organisms are found in the scrapings and smears made from the blood obtained from the sores. The fact that the organism was not demonstrated in this case may be accounted for by the fact that the lesion was involuting, and it is a known fact that as the sores get better the organisms tend to disappear. The patient had improved 50 per cent. since he was first observed, and it was doubtful as to whether the organism could now be found.

DR. HIGHMAN suggested the use of Romanowsky stain.

DR. CHARGIN said he had used the Wright, Giemsa, as well as the Romanowsky, stain.

LUPUS ERYTHEMATOSUS? Presented by DR. ABRAMOWITZ.

A. M., 46 years old, a Russian, street cleaner, presented himself at Dr. Fordyce's clinic with an eruption confined to the scalp, cheeks, nose and ears, of fifteen years' duration. The patient exhibited an eruption of the regions mentioned consisting of well-defined erythematous lesions covered with fine white scales, and atrophy. He also showed destruction of the helix of the ears and ectropion. No subjective symptoms were present.

DISCUSSION

DR. WILLIAMS said that the scalp presented the typical picture of lupus erythematosus, whereas the appearance of the nose was typical of lupus vulgaris; the border with the brown pigmentation looked like lupus vulgaris; there were definite ulcerations on the ear and face; and the man gave a history of having frequent ulcerations, which was not characteristic of lupus erythematosus but of lupus vulgaris. It was possibly a case of both lupus erythematosus and lupus vulgaris. He had lupus erythematosus and probably lupus vulgaris also.

DR. POLLITZER said the man had lupus vulgaris so far as the lesions of the face were concerned. Lupus erythematosus did not produce that amount of destruction. The upper part of the right ear was damaged to an extent never caused by lupus erythematosus. He had been surprised to hear that the diagnosis of lupus erythematosus had been made. It impressed him as a typical case of extensive old lupus vulgaris of the face. On the scalp the condition resembled lupus erythematosus, and it was possible that there was a combination of the two.

DR. HOWARD FOX felt that a case of this type could be indefinitely discussed without arriving at any unanimity of opinion. Some would consider it lupus vulgaris and others lupus erythematosus. He thought the question might be settled by the microscope. His personal opinion was that clinically the disease was lupus erythematosus. He thought that the entire eruption was either one disease or the other and did not like to straddle the question by suggesting that one part of the eruption was lupus vulgaris and another lupus erythematosus. The number of cases of the two diseases occurring simultaneously in the same person was extremely small.

DR. LANE asked whether the microscopic diagnosis of the lesions on the face could settle the question if no apple jelly nodules were found.

DR. GILMOUR suggested that a microscopic diagnosis should be made and the result reported at the next meeting.

DR. LEVIN said that the question in his mind was whether the deformity resulted from destruction of tissue or whether it resulted from pressure of tense or shrinking skin covering hard tissue like the cartilage of the nose and ears, as in this case. He regarded this as a case of lupus erythematosus.

DR. HIGHMAN said he had not seen the case, but in connection with the microscopic study of these lesions, he wished to caution against placing too much faith in the microscope. To do the work properly one would have to take specimens from two different areas and study them; the microscopic structure of lupus erythematosus was not always convincing, as was that of lupus vulgaris, but if negative evidence were found in a specimen from the scalp one could not be positive that he was not dealing with an inflammatory process near the lupus vulgaris lesion that had nothing to do with the tuberculous tissue itself. One case of the combination of lupus vulgaris and lupus erythematosus was published in the *Archiv für Dermatologie*, January, 1909.

URTICARIA PIGMENTOSA. Presented by DR. ABRAMOWITZ.

J. T., 5 months old, of Italian parentage, was brought to Dr. Fordyce's clinic with the history that the eruption had been present for four months. The lesions were numerous on the back and extremities, and were split-pea to almond sized, of a yellowish-brown color and showed urtication on friction.

A biopsy revealed the usual structure of urticaria pigmentosa, with mast cell infiltration.

SYPHILOMA VULVAE. Presented by DR. LEVIN.

A young woman of 20, was first shown in May, 1919. She stated that for the last six months she had noticed a large swelling, growing larger and larger. She said that she had no pain and no discomfort, and her general condition was in no way influenced by the growth. The present picture was somewhat different from that when she was first seen, when there was one hard parchment-like pendulous tumor hanging down between the thighs, the size of a child's fist, originating in the labium. Where the tumor touched the labia majora there were ulcerations. The blood examination on two different occasions gave a +++ and ++++ Wassermann reaction. Dr. Fox was asked to look at the patient, and he too made a clinical diagnosis of syphiloma—a tertiary manifestation of syphilis. The procedure at that time was to excise all of the affected area, which was done without any trouble, and at the same time to give the patient intense antisyphilitic treatment—intramuscular injections twice weekly. She left the hospital earlier than was thought wise, and half a year later came back with a similar condition; she was again operated on and again left the hospital earlier than advised; she then came back and received antisyphilitic treatment, and for the first time the Wassermann reaction was negative. The patient was presented for suggestions as to treatment.

DISCUSSION

DR. MACKEE said that he did not feel capable of discussing the subject he was about to broach, for he had never seen any of these cases; but he would think seriously of ulcerating granuloma. Dr. Goodman, who had seen some cases in Porto Rico, might say a few words in regard to it.

DR. GOODMAN said that the case resembled clinically the cases of ulcerating granuloma which he had seen in the tropics. The character of ulcerations with cicatrization and the hypertrophy through which hairs appeared were suggestive. The invasion of the vagina and the beginning ulceration of the anterior border of the anus were such that he was inclined to think that ulcerating granuloma was the condition presented. Bacteriologic studies would disclose either the *Calimatobacterium granulomatis* of Donovan, or the *Spirochaeta aboriginalis* of Wise. The biopsy would also aid in the diagnosis. He had reported his cases in full soon after his two years' tour of duty in the tropics.[1]

DR. HIGHMAN said that among other things to be considered was the possibility of the patient having a cicatrization following syphilis, with local elephantiasis.

DR. STEIN asked what therapy Dr. Goodman would suggest.

DR. GOODMAN advised antimony and potassium tartrate (tartar emetic) given in 1 per cent. solution intravenously. Five c.c. may be given every other day; if 5 c.c. are diluted to 25 c.c., the pains along the arm of which the patient may complain are avoided.

HODGKIN'S DISEASE OF THE SKIN. Presented by DR. WISE.

M. G., 21 years of age, born in the United States, married, no children, presented herself at Professor Fordyce's clinic about ten days previously, complaining that about two years ago she began to have some itching. This was followed by swollen glands and the appearance of an eruption all over the body except the face, scalp and legs. She presented a papular and scratched eruption on the trunk and upper extremities, associated with enlarged glands of the neck, axillae and groins. She had received many roentgen-ray treatments for the glands. The patient stated that one of the glands had been excised and showed Hodgkin's disease. The skin condition was improving under roentgen-ray treatment.

DISCUSSION

DR. HOWARD FOX said that the case might be considered one of Hodgkin's disease from the microscopic findings in the gland, though the clinical symptoms were not well marked. The eruption was of a prurigo-like type, frequently seen in both leukemia and Hodgkin's disease. They were the lesions that showed simple inflammatory changes, and not those characteristic of Hodgkin's disease. These cases of prurigo, as well as those of urticaria and pruritus, were probably toxic manifestations of the disease. When occurring in leukemia they had been termed leukemides by Audry.

DR. FRASER said that these prurigo-like eruptions were sometimes associated with Hodgkin's disease; but as Dr. Fox had stated, the histologic picture was neither that of leukemia nor of Hodgkin's disease, but an ordinary prurigo eruption. In other words, these lesions anatomically are not the Hodgkin's gland lesions. They are present as a complication.

DR. HIGHMAN said it was an unusually interesting case, for it brought to the fore in 1920 a condition established in Vienna in the eighties, described by Hebra and Kaposi as prurigo lymphatica, including the leukemias and Hodgkin's disease, or pseudoleukemia. The lesions were prominent on the flexor rather than on the extensor surfaces, which was characteristic, as opposed to the findings in typical prurigo. The case was not of the type that Audry

1. Arch. Dermat. & Syph. **1**:151 (Feb.) 1920.

called the leukemides, but rather belonged to the true leukemic infiltrations. The former lesions were not characteristic of leukemia in their histologic structure; the latter were. He recalled two or three instances in which the histologic examination of the skin aroused suspicion of leukemia, later corroborated by the general findings. In this case there was a definite leukemic infiltration of the skin, and a clinical condition which European dermatologists would recognize without difficulty.

DR. WISE said that one of the interesting features of the case was that the patient gave a definite unmistakable history of having had enlarged glands which disappeared under roentgen-ray treatment, and subsequent to that therapy the skin disease appeared. One would not expect the lesions to come on after the disappearance of the glands. That impressed him as rather peculiar.

FOR DIAGNOSIS. From the service of Dr. Trimble, New York Skin and Cancer Hospital. Presented by DR. ROTHWELL.

The patient, a white man 56 years of age, presented over the dorsum of the trunk the dried crusts of pustules which had appeared two or three days after a slight fever and feeling of general malaise. He at the outset of his disturbance, noticed slight pain in the scapular (right) region, and at the outbreak of his pustular eruption he had experienced a slight chill.

The eruption, when first inspected, consisted of pustules generously distributed over the back, from the root of the neck to the waist, on distinctly erythematous bases. The limits of the eruption were posterior to the mid-axillary lines. A few pustular lesions were to be seen at this first inspection, distributed over the shoulders and on the outer aspects of the arms. The lesions had dried down under applications of simple boric acid ointment. There had been no other subjective symptoms than a feeling of contraction in the affected region.

DISCUSSION

Several of the members expressed agreement with the diagnosis of pustular folliculitis.

DR. ROTHWELL said he had not expected the case to attract so much interest. A number of physicians thought that it was simply a pustular folliculitis, but the diagnosis of double herpes zoster had been made by others.

DR. HIGHMAN thought the case looked like neither single nor double herpes zoster; clinically, it was suppurative folliculitis. In his opinion not much reliance could be placed on the patient's statement that no local applications had been used.

DR. WILLIAMS said there was a marked contradiction in the history. It was stated that the patient had had the eruption eight days only, and yet there were pale scars which could only result from lesions which had healed several weeks before.

A PRELIMINARY REPORT ON SILVER ARSPHENAMIN.* DR. MIRAN B. PAROUNAGIAN.

Silver arsphenamin was first suggested by Ehrlich. The synthesis of this compound was completed by Kolle in 1918.

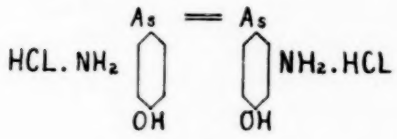
The drug was first tried by Wechselmann at the Speyerhaus, at Frankfort-am-Main. It has since been extensively used at many clinics in Germany.

* From the Department of Syphilology, Bellevue Hospital.

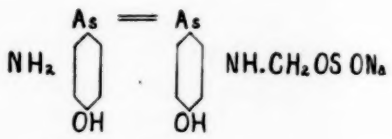
Reports of it are numerous in the German literature, and are practically unanimous in its praise. A résumé of the literature is reserved for a later communication.

The structural formula of silver arsphenamin is still under discussion by scientists abroad, particularly as regards the location of the silver in the molecule. There is no doubt, however, that the silver is actually chemically combined and not present in the product as finely divided or colloidal silver. The silver content is approximately 14 per cent. and the arsenic about 22 per cent.

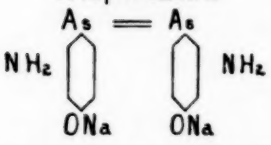
For purposes of comparison the structural formulae of the various arsphenamin compounds are given:



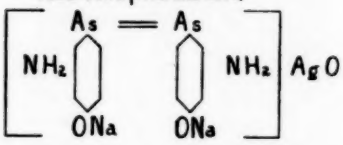
Arsphenamin



Neo-Arsphenamin



Sodium Arsphenamin



Silver Arsphenamin

In the formula for silver arsphenamin, it will be noticed that the entire molecule has been bracketed and the silver placed outside, indicating that its exact location has not yet been determined.

The dosage recommended by German investigators is from 0.1 gm. to 0.3 gm., and the intervals of treatment from twenty-four hours to four days. The number of injections is from eight to sixteen, according to the stage and resistance of the disease.

Through the courtesy of the H. A. Metz Laboratories, we have had the opportunity of administering silver arsphenamin made in America, according to the original formula.

Up to date, we have given 373 injections to 107 patients during a period of eight weeks. The dosage has varied from 0.05 gm. in children to 0.3 gm. in male adults. The dilution at first was 50 c.c. of 0.4 per cent. saline solution to each decigram. Later the dilution was decreased to 30 c.c. to each decigram. No difference in the action of the drug was noticed following this change in technic.

At first doses were given once weekly; later at five-day intervals, and more recently as often as every second day. The largest number of doses given to one patient has been eight, with a total dosage of 1.8 gm. The average patient has received to date about 1.5 gm., excluding those who have come under treatment within the past two weeks.

Patients with active lesions, who had received no previous treatment, were first selected in order to test clinically the therapeutic efficacy of this drug. Primary cases selected were positive for the *Spirochaeta pallida* by dark-field examination. The secondary cases were typical.

More recently patients with older and previously treated cases have been treated with this drug, although it has been our purpose to limit the use of silver arsphenamin to persons in whom the improvement could be determined clinically.

Early primary lesions of syphilis have responded with unusual rapidity to silver arsphenamin: within twenty-four hours the lesions have shown marked regression. In secondary cases ordinary roseolas have disappeared after one or two doses. Papular and pustular lesions have responded with gratifying rapidity. Mucous membrane lesions have been slightly more resistant. In late syphilis, ulcerating gummas, nodular syphiloderms and bone lesions have all responded satisfactorily to silver arsphenamin.

"Table reactions" have never occurred. Later ill effects have been uncommon, and in no case have they been serious. Mild headache, chill, nausea, vomiting and gastro-intestinal discomfort have occasionally been reported by patients, but these have always been of a mild type and in no instance was the course of treatment interrupted because of these by-effects.

In no case has mercurial treatment been combined with silver arsphenamin. Whether mercurial treatment will later be included in the routine is still under advisement. Reports from abroad are contradictory on this point.

The serologic result following the use of silver arsphenamin will not be considered in this preliminary report because, in our opinion, it is still too early to make any positive statement.

Summary.—1. Silver arsphenamin of American manufacture has been administered 373 times to 107 patients.

2. Uncomplicated primary lesions have shown marked improvement within from twenty-four to forty-eight hours.

3. Skin manifestations of the generalized period have been readily amenable to this drug.

4. Mucous membrane lesions of early syphilis have not disappeared with the same rapidity as the skin lesions of the same stage.

5. Later syphilitic manifestations improve satisfactorily under silver arsphenamin therapy.

6. None of the immediate table reactions nor the more serious later ill effects mentioned in the literature have been encountered in this series.

Conclusions.—In our hands silver arsphenamin has proved an effective addition to the arsphenamin series. Its small dosage, ease of administration, absence of ill effects and favorable therapeutic action will commend its further use, particularly by those adept in the use of other arsphenamin preparations.

Whether future experience will approve the use of silver arsphenamin alone or in combination with mercurial treatment remains to be determined.

DISCUSSION

DR. GOODMAN said that he had had the opportunity, through the courtesy of Dr. Phillip Grausman and Dr. Leo Michel, of using the German silver arsphenamin, and that he had with him several ampules of the drug which the members might care to examine. The drug had recently been brought over, and he had given it to seven patients. Two of them with primary lesions had shown improvement in a short time. A third patient with pustular secondary syphilis had improved in a manner which he had not seen exceeded by arsphenamin, except when that drug was given according to the method of Dr.

Pollitzer—three doses in forty-eight hours. Another patient with a ++++ Wassermann reaction and possibly syphilitic disease of the sinuses had been given a dose on Sunday, and complained of a headache from Sunday to Monday morning. He regretted that roentgen-ray pictures of this patient prior to and after the injection were not available. No ill effect had been noted in connection with the injections of silver arsphenamin in the short experience he had had.

The German literature had mentioned many accidents following this drug. Allowing any of the solution to flow outside the vein and into the tissues was supposed to be attended with grave results. In several cases reported the drug had been given over long periods—sixteen to eighteen injections, and then by-effects were noted. On the whole, the reports had all been favorable.

DR. WISE said that what interested him was the question of argyria, and he would like to know what Dr. Parounagian had to say on that subject.

DR. BECHET wished to ask Dr. Parounagian if in his estimation the therapeutic results from silver arsphenamin were more satisfactory than those attained with arsphenamin; he had not mentioned this fact in his paper. Dr. Parounagian also spoke of the truly remarkable therapeutic results obtained in the short period of from twenty-four hours to two or three days; this was just as true for arsphenamin. Dr. Bechet recalled seeing a patient that same week with a large nodular serpiginous syphiloderm, several inches in diameter, to whom 0.9 gm. of neo-arsphenamin was administered. Within forty-eight hours the lesion had involuted more than 50 per cent. Dr. Parounagian had had some moderate reactions; these were becoming less and less frequent after the administration of arsphenamin. For the past two years not the slightest reaction had been observed by him; 0.9 gm. of neo-arsphenamin and 0.6 gm. of arsphenamin were the practically invariable doses.

DR. HIGHMAN said that the section should thank Dr. Parounagian for directing attention to the silver member of the arsphenamin group. He foresaw, however, danger in a new era of overenthusiasm followed by depression, such as had been gone through with arsphenamin. It reminded him of Perkins' metallic tractors which Oliver Wendell Holmes wrote about, and turtle bacilli —the only thing that would justify the introduction of a new preparation representing a material advance—something that could not be determined without statistics on which to base reasonable conclusions. The crux of the situation was: Was there less danger in the new than in the old salt; and did the lesions improve more rapidly, not just as rapidly? Why should a preparation that heals mucous lesions less rapidly than the old one be better, particularly since mucous membrane is more vascular than skin, which would justify the expectation of their more rapid involution than the skin lesions, as experience indicated with the old preparations. This seemed irreconcilable.

Dr. Highman said he could not gather any clear idea of Dr. Parounagian's time estimations; but that last Tuesday he had given a woman with a primary lesion on her hand and a florid secondary eruption, an injection of 4 dg. arsphenamin, and that by Friday the eruption had faded 80 per cent., and (if one could talk in such terms) the chancre had decreased by half in this same seventy-two-hour period. Were Dr. Parounagian's results any better than that?

DR. MACKEE said that silver arsphenamin was being used experimentally at the clinic, but they were not yet prepared to give out the results. Naturally he

was interested in this report by Dr. Parounagian, but was not much impressed with the results reported. It is curious how any new drug gives better results for a while, and later the results prove to be not so good. From what he had seen and read and heard, we have a drug that compares favorably with arsphenamin. About the danger, very little could yet be said. The question of argyria was an important one. We are getting keratoses from arsphenamin given a few years ago; and we may get argyria from using silver arsphenamin.

Dr. Abramowitz said that in a conversation with Dr. Fordyce last spring regarding silver arsphenamin, the latter said that the possibility of argyria developing was to be considered. Lochte reports such a case of argyria, an abstract of which appeared in a recent issue of *The Journal of the American Medical Association*. The original case report was in the *Therapeutische Halbmonatshefte* **34**: (June 15) 1920.

Dr. MacKee said it was interesting to note the points of difference in observation. He had seen patients who had improved from 33⅓ per cent. to 150 per cent.; others say the patients do not improve at all. There is always a difference in the observations. Dr. Parounagian had just asserted that he had seen a chancre practically disappear within twenty-four hours. That seemed to be a biologic impossibility. He did not see how any lesion the size of a dime could undergo involution in twenty-four hours.

Dr. Highman said he wished to corroborate the remark made by Dr. Lane. In 1915, when he was still working at Cornell University, a faculty rule had been passed forbidding larger doses of arsphenamin than 2 dg. Every one had been astonished to note that the results were precisely the same as with larger doses. Dr. Marsh had reported the findings with these minimal doses in one of the New York medical periodicals. With such small doses were produced the same effect on all lesions as had been obtained from double the dose. Referring to Dr. MacKee's remarks about the disappearance of the chancre reported by Dr. Parounagian, Dr. Highman said that he also would like to know how a globule of infiltration the size of a small marble could be absorbed so soon, except under the eyes of enthusiasm.

Dr. Parounagian said, in reply to Drs. MacKee and Highman's remarks regarding the chancre healing in twenty-four hours that he was misunderstood, as he stated as follows: "Within twenty-four hours the lesions have shown marked regression." He conscientiously believed that the results from silver arsphenamin were far superior to either arsphenamin or neo-arsphenamin, either domestic or imported, and invited the gentlemen to visit his clinic and observe the cases.

As to Dr. Fred Wise's inquiry regarding argyria cases, he stated that he had seen an abstract of a case in *The Journal of the American Medical Association* from an article by Lochte, *Therapeutische Halbmonatshefte*. The patient had received seven neo-arsphenamin injections and ten months later developed tertiary lesions. Later he received twelve silver arsphenamin injections, the first injection intramuscularly; five days later icterus developed and in spite of that the injections were continued; a few days later argyria developed. Dr. Parounagian said, taking into consideration thousands of injections that have been given in Germany, the one or two cases of argyria reported was not as serious as the number of deaths reported from the use of arsphenamin and neo-arsphenamin.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Regular Monthly Meeting, Jan. 10, 1921

MILTON B. HARTZELL, M.D., *Presiding*

LICHEN PLANUS. Presented by DR. HARTZELL.

A white girl, 10 years of age, developed an eruption last July, which rapidly became generalized, though the face, hands and feet have remained relatively free. Until a few days before presentation, when she came under the speaker's observation, she had received no internal medication, using only a liniment prescribed by the attending physician. At first the rash was very itchy, but later that symptom abated somewhat. The outbreak consisted of almost innumerable pinhead sized shiny papules and pigmented areas from which similar lesions had disappeared. The present papules and stains of former ones were definitely grouped into areas 0.5 to 1 cm. in diameter, the groups being equidistant from one another, about a centimeter apart on the back, where they were most abundant. In some places distinct rings were seen but there was no linear arrangement or umbilication. There was a slight degree of elevation of the lesions, which was most apparent on the trunk, especially posteriorly. The outbreak on the extremities was much fainter and less thickly-set. Scaling was slight or absent. The speaker had never seen a similar case. He considered it an atypical lichen or lichenoid eruption.

DISCUSSION

DR. SCHAMBERG said he had never seen a similar case, at least in a child. Many of the papules had a perifollicular position.

DR. ROSE HIRSCHLER asked Dr. Hartzell the age of the youngest patient with lichen that he had seen. He replied that he could not answer definitely, but that he had never seen it in infancy. In this case there was a fine stippling due to atrophy about the mouths of the follicles. There was no mucous membrane involvement. The case was unique in his experience.

STRIAE ATROPHICAE. Presented by DR. STRAUSS.

The patient was a well built man of 24 without an excessive deposit of adipose tissue. He had not varied more than 3 or 4 pounds in weight since the eruption was noticed, and he had at no time taken on weight rapidly. In March, 1920, he first noticed the eruption which had appeared on the inner aspects of both thighs. When seen at that time it consisted of slightly depressed purplish and reddish streaks, running somewhat transversely and corresponding roughly to the lines of cleavage of the skin. Since that time they had paled considerably, and bore more resemblance to depressed, stretched scars. There were no subjective symptoms, and there was no similar eruption on the lower abdomen or other portion of the body. The case was shown, not so much for diagnosis as for explanation of its appearance in this region apparently without cause. Those present offered no opinion.

ATROPHODERMA PEMPHIGOIDES. Presented by DR. GREENBAUM for DR. SCHAMBERG.

The Jewish woman, aged 55, shown at the November and December meetings of the society, was the patient. After three months' observation the

attendants had finally been able to overcome her prejudices sufficiently to allow them to aspirate one of the lesions on her leg. Some bloody serum escaped. Until that time, there had been some doubt among the members as to whether the lesions were really blebs. Only a few drops of contents escaped as the bleb was somewhat flaccid.

DISCUSSION

DR. HARTZELL still hesitated to classify the eruption or the lesion as a bleb on account of its peculiar characteristics.

DR. SCHAMBERG agreed that it was not an ordinary bleb, but felt that the name atrophoderma pemphigoides was applicable to the condition; a bleb followed by atrophy, the latter deep and the lesions remarkable. Dr. Hartzell added that it did not appear to be an inflammatory lesion.

DR. HIRSCHLER had not seen the case before. She remarked on the sensation of an edge produced when the finger was passed over the lesions—a buttonhole left by the deep atrophy.

DR. GREENBAUM added that the condition was now in its third year. Occasionally, new blebs had made their appearance while the patient had been under observation, and these ran an indolent course. Even the smallest ones had the same quality as the large ones—deep atrophy in the corium. Individual lesions had lasted at least three months.

DR. SCHAMBERG remarked that to some it might suggest an adult case of epidermolysis bullosa, but in the latter disease there would be a history of injury and the blebs would be superficial.

DR. HARTZELL ended the discussion by saying that it was all guesswork without a biopsy, consent for which procedure would be almost impossible to obtain from this patient, judging by the length of time necessary to effect aspiration of a bleb.

ATROPHIA CUTIS. Presented by DR. CORSON.

A waiter, Russian by birth, who had been seen that day for the first time, had had several attacks of gonorrhea—one or more during the course of the skin condition. This outbreak was limited to the glans penis and the sulcus behind it. The patient said it started as reddish, scaly areas on the glans and gradually covered its surface. Later the color faded, the scale disappeared and when shown the skin of the glans was thinned, loose, crackled and somewhat shiny. In addition, there were a number of small depressed scars on the surface. The patient was circumcised in infancy, and insisted that he had kept the glans clean when he had a urethral discharge. No caustics had even been used on the penis.

DISCUSSION

DR. SCHAMBERG said the condition resembled scarring due to superficial erosive action.

DR. HIRSCHLER said she had noticed such superficial scarring of the genitalia in women—both gonorrhea and chancroidal cases.

CASE FOR DIAGNOSIS. Presented by DR. KLAUDER.

A mulatto woman, aged 25 years, presented a maculopapular rash, generalized in distribution and of three months' duration. She had originally undergone treatment as a syphilitic patient and had received thirty injections of

arsphenamin when the present outbreak appeared. Since that time, seven more injections had been given. The lesions scattered over the body were not numerous, probably not exceeding twenty-five. They ranged in size from that of a pea to that of a large lima bean. In color, they were dark reddish-brown with a well-defined scale. Itching was complained of, and the lesions were lightly excoriated. They were somewhat elevated and plaque-like. The trunk and arms were the seat of most of the lesions.

DISCUSSION

DR. SCHAMBERG brought up a point of interest as to whether there was any relation between the arsenical treatment and the eczematoid dermatitis en plaque which this condition resembled. If caused by the drug, the lesions would, following its withdrawal, tend to disappear and later recur at the same place on resumption of treatment, acting as a danger signal preceding a generalized outbreak. Here the eruption resembled more the eczematoid type in that it was unaffected by arsphenamin treatment.

DR. KLAUDER said a cutaneous test for arsphenamin sensitization had been employed with negative results.

DR. HARTZELL thought it unusual that an acute arsenic dermatitis should occur in circumscribed patches. The lower part of the legs was free from eruption. General adenopathy was still present.

DR. SCHAMBERG said that organic arsenic preparations sometimes affected small areas of skin, citing the instance that the backs of the fingers sometimes show patches of dermatitis, no other region being affected.

DR. C. N. DAVIS remarked that the case resembled the so-called parasitic eczema of some European observers.

DR. KLAUDER explained that this patient had received no mercury. Following extravasation, there was a patch of pigmentation with some thickening at the bend of the elbow. At the December meeting, Dr. Schamberg had pointed out the possibility of cases of arsphenamin dermatitis having been sensitized in this manner. This patient was unaffected by subsequent treatment—neither better nor worse. The dosage was 0.6 gm. arsphenamin throughout.

ACNE NECROTICA. Presented by DR. GREENBAUM.

A short, stout, Jewish girl of 12 years had an eruption of one year's duration, situated on the upper part of the back and on the forehead at the hair margin, scattered from ear to ear. The back showed nothing but the depressed scars where active lesions had recently existed. These cicatrices averaged the size of a split pea. On the forehead flat, crusted lesions were interspersed with other depressed scars of a slightly smaller size. When first taken under observation, the pustules on the back were active and were seen to heal and change into the present formations.

DISCUSSION

DR. HARTZELL said he had never seen such large cicatrices resulting from this disease. The scars were clearly due to this eruption as some active and infiltrated lesions could still be seen. They were papules with a necrotic center which left a central pit. There was none on the hands where papulonecrotic tuberculid was frequently found.

DR. GREENBAUM found the *Staphylococcus aureus* in cultures from the lesions.

DR. SCHAMBERG remarked that this appearance was frequently seen in Russian emigrants in some of which he had suspected an infected varicella at

some previous time. The small follicular pits in the larger depressions made them look not unlike vaccination scars. They were not in the group with papulonecrotic tuberculids, and he did not regard them as tuberculous in origin.

DR. HARTZELL felt that there was apparently some relation between the two conditions, but so far he had not been able to trace it. The lesions were not like the papulonecrotic tuberculid on the hand.

DR. SCHAMBERG observed that acne necrotica is cured in a relatively short time. It responds readily to roentgen rays and vaccines. This is not the case with the papulonecrotic tuberculid which is more resistant. Among other diseases of the skin caused by the tubercle bacillus or its toxin, he felt that lupus erythematosus should be included. He was more and more persuaded to believe that this was the case. It was hard to remove this factor in the face of the knowledge that 90 per cent. of mankind have or have had the disease. Whether it was the first or second factor in the causation, he did not know.

DR. HARTZELL said that he had had cases of lupus erythematosus in persons with excellent physique, the disease lasting thirty years in one instance. He did not believe it was due to tuberculous infection. Against the fact of almost universal infection can be advanced the argument that in that case, the disease should be much more common. Many cases were undoubtedly aggravated or known to occur after sunburn.

DR. SCHAMBERG reported that the negro with the prurigo-like eruption, enlarged lymph nodes and lipomatosis, shown at the November meeting had an eosinophilia of 58 per cent. which later fell to normal and subsequently rose to 43 per cent. The eruption was accentuated at the time of the paroxysm of eosinophilia.

Book Review

VENEREAL DISEASES, THEIR CLINICAL ASPECT AND TREATMENT. With an Atlas of 108 colored and 21 halftone illustrations. By J. E. R. McDonagh, F.R.C.S. St. Louis, C. V. Mosby Company, 1920.

McDonagh has given us a companion volume to his earlier book, "The Biology and Treatment of the Venereal Diseases," which was published in 1915. Like the first volume, it is an expression of personal opinion. He starts in directly with the "leucocytozoon syphilidis" etiology of syphilis without any preliminary statement for the many persons who may be unacquainted with McDonagh's generally unaccepted theory of the sexual and asexual cycles of this supposed organism.

The clinical material on which the book is based appears to be uncommonly great in amount and comprehensive in character. Every phase of syphilis is considered. The drugs used in the treatment of syphilis include, besides mercury and arsphenamin, the various preparations which McDonagh has exploited. His therapeutics are as queer as his microbiology of syphilis and as little in accord with accepted views. The book cannot be recommended to the unitiated in the knowledge of syphilis. It is more or less stimulating to the expert from the very fact of its radical views. If McDonagh is in step the rest of the regiment is certainly out of step.

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